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THE INTERNIST AT WAR; A GLANCE AT THE RECORD *

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THE military aspect of this program has a natural, vital appeal to us and we are fortunate to have men on it whose accomplishments and whose experience in the field mark them as experts in the topics they have and will discuss. From Colonel Holbrook we have heard of the accomplishments of our Army Air Forces in the important field of evacuation. We hear much, too, of the achievements of our surgical colleagues—their extraordinary accomplishments on the battlefield and in the surgical hospitals behind the fighting fronts. We are duly impressed by their ability to save lives which in the last war they could not save. Those of us who saw men die by the score in evacuation hospitals from shock, gas gangrene, and sepsis can fully appreciate the triumphs of 1944 war surgery. The 1917 supply of well trained Army and Navy surgeons has been multiplied many, many times in the 1944 Army and Navy. Thanks to the improvements in medical education and postgraduate training of the past twenty-five years, good surgery is commonplace and *not* exceptional in Army hospitals in the forward areas. Shock in 1944 can be, and is, treated effectively at the front, thanks to physiologically minded surgeons and to readily available blood substitutes. Sepsis no longer kills commonly because it is prevented and cured by good surgery, sulfonamides, and penicillin. Therefore, it is no wonder that an enormous number of battle wounds which do not kill outright are now, in this war, for the first time within the effective range of surgical treatment. The death rate for battle casualties now, in World War II, is 3.3 per cent; it was 8.1 per cent in World War I. Thus, the surgeons save 97 out of 100 wounded men who are admitted to Army hospitals. We join with them in rejoicing, and we congratulate them on these extraordinary achievements.

During this war the preventive medicine program of the United States Public Health Service and of the Armed Forces has been amazingly success-

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ful, too. Among our troops the incidence of lethal disease has been kept at a level which establishes a new low for any army in any war in history. In spite of the fact that the Army and Navy are scattered over the world, and in regions where disease is rife, yellow fever, louse typhus, typhoid, leprosy, schistosomiasis, plague, and other threats have not materialized. The health of our Army and Navy is better than at any time in their existence. For this we acclaim the preventive medicine services—civilian and military—and we do it wholeheartedly and with unbounded enthusiasm.

But what of internal medicine in this war? In spite of all that has been said about the surgeons, we know that many of the men whose lives are now saved by them will not fight again—and our *fighting* men are the men who will win this war. The chief objective of the Army and Navy Medical Departments is to maintain the highest effective rate possible in combat units, and this is done chiefly through preventive and curative medicine. In spite of an extraordinarily good preventive medicine record, disease *has* occurred. When it occurs, the internists go into action. What is their record in this war?

As is to be expected, internal medicine has established a record of accomplishment in the Army and Navy which reflects the extraordinary achievements of the past twenty-five years in civilian practice. Those of us here who, in 1917–18, took care of soldiers and sailors with sinusitis, bronchitis, pneumonia (lobar and post-influenzal), cerebrospinal meningitis, septic disease, tuberculosis, dysentery, syphilis, gonorrhea—to mention the diseases most frequently encountered in military practice—will appreciate the significance of the following figures. Obviously, they are neither absolutely accurate nor final—nevertheless, they are both informative and significant.

Meningitis	World War I	Fatality: 38%
	World War II	Fatality: 4%
Pneumonia	World War I	Fatality: 28%
	World War II	Fatality: 0.7%
Tuberculosis	World War I	Fatality: 17.3%
	World War II	Fatality: 1.8%
Dysentery	World War I	Fatality: 1.6%
	World War II	Fatality: .05%

What of the omnipresent problem of the venereal diseases in the Army? You will be relieved to learn that in this war the venereal diseases have finally made good their escape from the awkward and, as we now view it, medieval clutches of the urological surgeon who, armed with sound, syringe, silver salts, irrigating can, and a long, strong index finger, indulged his naive faith in irrigations and dilatations of the posterior urethra and chiropractic manipulations of the prostate and seminal vesicles. Nowadays gonorrhea is being allowed to remain a simple pyogenic infection of the anterior urethra, the secretions from which are provided, by the good God, with natural drainage and with frequent physiological irrigation. I am happy to report that at last in the Army the venereal diseases are officially assigned to the

beneficent care of the internist. As a result, the complications of gonorrhea have become practically nonexistent. The figure for days lost from duty because of the venereal diseases is already 33 per cent less than in World War I and continued improvement is confidently anticipated.

Finally, let us examine the record of preventive and curative medicine in this war as reflected in the

Annual Death Rate per 1000 for all diseases in the Army, excluding surgical conditions:

World War I	15.6
World War II	0.6

This is a way of saying that a division of 10,000 men in 1918 would experience 156 deaths per annum from diseases (excluding injuries). This same division in 1944 loses 6 men by death from disease. This is a reduction in death rate greater than 95 per cent!

What are these extraordinary results due to? They are due to

1. High level of professional competence in internal medicine in the Army.
2. Careful placement of this professional competence where it will do the most good in the Army.
3. Provision, for medical officers, of adequate diagnostic and therapeutic facilities with which to work.
4. The extraordinary devotion to duty of Army and Navy doctors.

Thus, in the Army and Navy Medical Department achievements in internal medicine, this College sees the fruit in the war effort of its long years of work—its efforts (*a*) to foster research which eventually provides the diagnostic and therapeutic tools; (*b*) to educate and train medical men in the use of these diagnostic and therapeutic tools.

This war will be won by effectives—men kept healthy by preventive medicine, and, when this fails, restored to health by internal medicine. The maintenance of the lowest noneffective rate possible is the chief objective of the Medical Departments of the Armed Forces. The therapeutic part of this task falls principally upon the internists. Our record in dealing with noneffectiveness thus far has been good. Indeed, as you have seen, it has been superb. It reflects in the Armed Services the extraordinary effectiveness of internal medicine as practiced in the United States. Let us, in civilian and military medicine, resolve to make it better by laboring earnestly and diligently, and with complete devotion to duty, in our important segment of the war effort.

OBSERVATIONS OF ATYPICAL PNEUMONIAS OF THE INFLUENZAL VIRUS TYPE*

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During the months of December 1942, January and February 1943, a series of cases of atypical pneumonias of the influenzal virus type was observed at the Elizabeth Steel Magee Hospital, Pittsburgh, Pennsylvania. Because of the high mortality rate encountered in this type of pneumonia and because of the unusual termination in fatal cases by the rapid development of generalized pulmonary edema, our interest was awakened by certain clinical observations to be presented. These observations are considered important because they indicate the necessity for revision of certain therapeutic measures, and because they are a definite aid in prognosis.

During the autumn months of 1942 the milder cases of influenza were encountered. These patients presented mild pharyngitis, malaise, low-grade fever, and generalized aching. The period of illness was from three to five days and was self-limited. However, in December 1942 the lower respiratory infections of the virus influenzal type became prevalent, and in the three months' period, mentioned above, 24 cases of pneumonia were observed.

In an analysis of these 24 cases of pneumonia, five patients had sputum positive for pneumococcus by the Neufeld typing method. All of these patients recovered, responding to the ordinary methods of pneumonia therapy. However, in three of these five cases the clinical course suggested a lower respiratory influenzal infection complicated by a pneumococcic secondary infection. The remaining 19 cases showed the typical syndrome of influenzal virus bronchiolitis and pneumonitis complicated by varying degrees of mixed infection. In eight of these 19 cases no sputum could be obtained because there was no productive cough. Of these eight cases, three were fulminating and fatal. The sputum of the 11 remaining cases all showed predominance of gram positive cocci resembling streptococci and pneumococci. Six cases showed sputum containing moderate numbers of influenza bacilli. The pneumococci in these cases were not sufficiently numerous to indicate advisability of typing them. No staphylococci were reported in any of these cases. None of the 19 patients responded satisfactorily to the accepted methods of pneumonia therapy.

The typical syndrome which was observed repeatedly showed a prodromal period of three to five days' duration, with malaise, mild pharyngitis, and low-grade fever. In three of the six fatal cases a disregard for the pro-

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dromal symptoms by the physician and patient had led to a fulminating infection resulting in death within 24 hours following admission to the hospital. The prodromal period was followed by the sudden onset of prostration, several chills, rise in fever, an aggravation of the generalized aching, and a hacking cough which was productive of scanty mucoid sputum. Varying degrees of dyspnea and cyanosis soon followed. Characteristically the examination on admission revealed a paucity of lung signs in relation to the degree of prostration. Roentgenographic examination in four early cases showed tracheobronchitis; in other cases it showed localized or scattered areas of increased parenchymatous density and hilar thickening. The leukocyte count on admission was usually a low normal with no apparent change in the differential count. Only two of the 19 cases showed a leukopenia. Later, as secondary invading organisms complicated the virus infection, there developed a leukocytosis of a varying degree with a corresponding increase of neutrophiles.

Of the 19 patients with influenzal virus pneumonia, six died, a mortality rate of about 31 per cent, corresponding to the mortality rate of the pandemic of 1917–1918.[1] The most interesting observation in all fatal cases was the development of a generalized and overwhelming pulmonary edema six to 24 hours before death. It was noted that prior to the pulmonary edema the heart sounds were notably feeble and following its development, the heart sounds became almost inaudible. Routine blood pressure readings taken at the time of admission and during the hospital course revealed a decline in blood pressure before the onset of the pulmonary edema. An elevation of the pulse rate above previous levels, and not in accordance with the temperature curve, was also found to precede the pulmonary edema. With these observations in mind, our attention was directed toward the early identification of the syndrome and the possible anticipation of the development of pulmonary edema in order that precautionary therapeutic measures could be undertaken. The accompanying table shows these circulatory changes as observed in the six fatal cases of virus pneumonia.

The pathological physiology accounting for these circulatory changes was graphically shown by the findings on two postmortem examinations. Both of these autopsies showed ulceration of the bronchi and bronchioles with peribronchial and lobular consolidation of an acute hemorrhagic type. There was destruction of alveolar tissue with areas of hemorrhage occupying the alveolar spaces. In American literature, little has been published concerning pathological changes of the heart associated with influenzal pneumonia. Post-influenzal myocardial damage and conduction defects have been noted,[2] but no mention of dilatation of the heart has been found. In both of the postmortem examinations the right heart was markedly dilated, and there was no evidence of previous valvular heart disease nor any history to suggest previous cardiac disease. One of these autopsies showed no microscopic myocardial changes; the other presented edema of the myocardium which has been described previously.[2]

In two of the cases, roentgenographic examination demonstrated a prominence of the pulmonic arc, and neither of these had any clinical evidence or history suggestive of heart disease. In one fatal case, venous pressures were recorded every hour from the onset of lowered blood pressure until death, and there was found a rise of six centimeters of water in the venous pressure. It is interesting to note in this connection that no significant change in venous pressure was recorded in a study made during the 1917–1918 pandemic.[3] There was noted a retardation of circulation as determined by repeated papaverine circulation times, but this was not in proportion to the rise of venous pressure.

From these clinical observations and pathological findings it is evident that the dangers of influenzal pneumonia are not only those of toxicity of the infection but also the mechanical and physiological disturbances of circulation. In the cases which terminated with the onset of pulmonary edema there was undoubtedly a generalized parenchymatous pulmonary edema, and in addition cellular and hemorrhagic debris and fibrinous exudates partially occupied the alveolar spaces. This resulted in a partial occlusion of the pulmonary vascular bed which produced a strain on the right heart. Evidence of right heart strain was presented by the postmortem findings of right heart dilatation, roentgenographic evidence of an increased pulmonic arc, and by changes in venous pressure and circulation time.

In accordance with this phenomenon of pulmonary vascular occlusion, it is quite probable that there is a definite decrease in the flow of blood from the pulmonary circuit into the left ventricle. This decreased inflow to the left ventricle plus possible toxic myocardial changes undoubtedly result in a decreased left ventricular output. The decreased output of the left ventricle plus toxic peripheral vasomotor disturbances result in a lowered blood pressure. By reflex action there is a rather sharp rise in pulse rate, for nature attempts to compensate for the decreased output per stroke by increasing the heart rate. It has been observed clinically that there is a progressive dyspnea as these changes take place. This is probably due to the progressive pulmonary disease. However, part of the increased respiratory rate may occur reflexly as a result of changes of pressure in the aorta and carotid sinuses, for it is pointed out by some physiologists that these structures possess sensitive nerve endings which reflexly increase the respiratory rate when the blood pressure is lowered.

As a result of clinical experiences and in view of the pathological physiology, we believe that certain precautions should be taken in an attempt to avoid or alleviate the mechanical and physiological disturbances of circulation even though there is little that can be accomplished to counteract the toxicity after the onset of the infection.

In the first place, in any endemic, epidemic, or pandemic influenza, it is of prime importance to confine to bed any patient with prodromal symptoms or symptoms of a mild influenza. The majority of patients in this series who succumbed to pulmonary edema were up and around until the time of

TABLE I

Clinical Observations of Six Fatal Cases of Virus Pneumonia

Case	Age	Sex	Days in Hospital	Blood Pressure			Pulse Rate			Heart Sounds			Duration of Pulmonary Edema before Death
				On Admission	6–8 hrs. before Onset of Pulmonary Edema	After Onset of Pulmonary Edema	On Admission	6–8 hrs. before Onset of Pulmonary Edema	After Onset of Pulmonary Edema	On Admission	6–8 hrs. before Onset of Pulmonary Edema	After Onset of Pulmonary Edema	
H.T.	47	M	1	135/86	135/86	110/60	120	140	160	Faint	Very faint	Inaudible	10 hrs.
M.F.	34	F	6	54/36	90/60	78/50	100	120	124	Faint	Moderate intensity	Faint	6½ hrs.
V.E.	60	F	1	132/78	110/68	90/64	90	106	116	Moderate intensity	Faint	Inaudible	12 hrs.
*M.B.	44	F	9	130/90	120/90	85/60	112	140	154	Low intensity	Faint	Very faint	6 hrs.
J.R.	40	M	13	128/88	116/82	90/62	80	130	120	Faint	Very faint	Inaudible	8 hrs.
L.B.	58	M	1	180/110**		140/82	140		140	Inaudible		Inaudible	?

* Postoperative influenzal pneumonia.

** Blood pressure recorded in column "On Admission" is the blood pressure obtained from the history since patient was admitted to the hospital in pulmonary edema.

hospitalization. Certainly bed rest will conserve a cardiovascular system burdened by an acute pulmonary infection. Those patients who continued up and around during the prodromal period and who survived showed more cardiorespiratory embarrassment and caused the physician more anxiety than the patients who were confined to bed immediately. This simple therapeutic procedure is one of the easiest and most efficacious, and certainly cannot be overstressed.

In the second place, it is important to start oxygen therapy early, before the onset of cyanosis and before the lower respiratory infection is well advanced. If the patient shows definite evidence of lung involvement or if there are changes in the blood pressure, pulse, or heart sounds as previously described, the clinician should prescribe oxygen. Oxygen may be administered conveniently by means of a nose and mouth mask at a rate of six to 12 liters per minute. An oxygen tent using six to 16 liters of oxygen per minute at a temperature of 60° F. to 68° F. is, in our experience, even more desirable. Oxygen under pressure, as suggested in a recent publication,[4] undoubtedly would be the most beneficial.

Because of the toxicity and severe prostration of these patients, many physicians administer fluids intravenously. The present study leads us to believe that such a clinical procedure is contraindicated. It is known that there is already a strain on the right heart, and the administration of fluids intravenously only adds to that burden. Four of the six patients who died had received fluids by vein, and it is believed that the development of pulmonary edema was hastened by this procedure. If fluids are not tolerated by mouth, then nasal gavage with feedings of four ounces of milk, four ounces of cream, and two teaspoonfuls of strained honey, alternating with the juice of two oranges and one lemon, two whole eggs, and two teaspoonfuls of strained honey. The feedings are warmed to 98° F. to 100° F. and are given every three hours. This diet provides 80 grams of protein, and certainly an adequate protein intake improves the patients' ability to fight infection. In addition, this procedure promotes diuresis and greatly diminishes abdominal distention. In some cases, nasal intubation may aggravate the dyspnea or prove unsatisfactory. Then proctoclysis or hypodermoclysis may be employed. Undoubtedly the patients presenting the changes in pulse, blood pressure, and heart sounds as described previously should not have any fluids administered intravenously.

Because of the strain on the right heart, the advisability of venesection is to be considered. Venesection was performed in one case, but the results did not warrant this as a routine procedure. The therapeutic effect of venesection is questionable.

No specific therapy is available at this time, but it is believed that the sulfonamides are indicated when there is evidence of the presence of secondary bacterial invaders. In all cases, absolute bed rest, adequate fluid intake, and an easily digested, well balanced diet containing an adequate protein intake, plus symptomatic and supportive therapy, are very essential. The

mortality rate of influenzal pneumonia may be modified favorably if, in addition to the above treatment, careful repeated clinical observations are made, oxygen is administered early, and fluids are not administered intravenously.

Summary

1. A series of 19 cases of influenzal pneumonia was studied, in which there was a fatality rate of 31 per cent.

2. The high fatality rate is accounted for by toxicity of the infection and mechanical and physiological disturbances of circulation as a result of partial occlusion of the pulmonary vascular bed, dilatation of the right heart, and a decrease of left ventricular output.

3. Repeated clinical observations of heart sounds, pulse rate and blood pressure in the presence of an influenzal pneumonia are stressed because they aid in the anticipation of development of pulmonary edema and indicate the necessity for certain therapeutic precautions.

4. Early confinement to bed, the early administration of oxygen, and the contraindication to fluids administered intravenously in cases of influenzal pneumonia are stressed.

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PRIMARY ATYPICAL PNEUMONIA, ETIOLOGY UNKNOWN: THE AVERAGE CLINICAL PICTURE BASED ON THIRTY-SEVEN ORIGINAL CASES *

By RICHARD H. SMITH, *Norfolk, Virginia*

THE increasing prevalence of an atypical form of primary pneumonia has commanded more and more attention during the past four years. Much of the literature on the subject is puzzling or contradictory. There is no "single criterion—clinical or laboratory—which characterizes the syndrome." [1] Diagnosis is arrived at by a process of eliminating similar diseases of known etiology and attempting to check the patient's signs and symptoms against those of groups of cases previously reported. Unfortunately the literature on the subject is still too fresh for the relative value of each sign and symptom to have been worked out. Yet from the present maze of apparent contradictions among reported groups of cases, there is emerging a clinical picture sufficiently clear-cut to permit reasonable diagnosis and tentative classification. The present study is based on 37 cases seen between January, 1941, and October, 1942 (12 other cases were seen but are not included because of insufficient data). This small series will serve to illustrate the clinical picture, as well as some of the variations in the literature.

Nomenclature. The disease shall be referred to in this paper as "primary, atypical pneumonia, etiology unknown." This is the designation assigned by the Commission on Pneumonia of the U. S. Army [2] and will probably apply to the largest standardized group of cases to be reported. Other designations to be found in the literature are "virus pneumonia, type A," [3] "acute pneumonitis," [1] "acute respiratory tract infection, type A," [4] "acute interstitial pneumonitis," [5] "bronchopneumonia of unknown etiology, variety X," [6] "current bronchopneumonia of unusual character and undetermined etiology," [7] "virus-type pneumonia," [8] "viral pneumonia," [9] and many others.

Etiology. The causative organism has not been identified. Attempts to demonstrate known rickettsias and viruses causing similar diseases such as influenza, psittacosis, and "Q-fever," have given negative results. Moreover the highest incidence of primary atypical pneumonia is in young adults. This age group is known to have the highest antibody titer to influenza virus, type A. Ferrets, susceptible to the influenza virus, are resistant to primary atypical pneumonia.[10, 11] From four cases Weir and Horsfall [12] isolated a filtrable agent in the mongoose which produced pulmonary lesions. By a laborious passage technic, they apparently were able to demonstrate neu-

* Read before the Norfolk County Medical Society, November, 1942. Received for publication January 4, 1943.

tralizing antibodies in the serum of convalescent patients. However, their results are rather inconclusive because of the apparent resistance of some of their animals to infection, and the failure of serial passage to increase virulence.

Virus etiology is still considered probable because of the contagiousness, the long incubation period of apparently 10 to 26 days,[6, 7, 8] the failure to

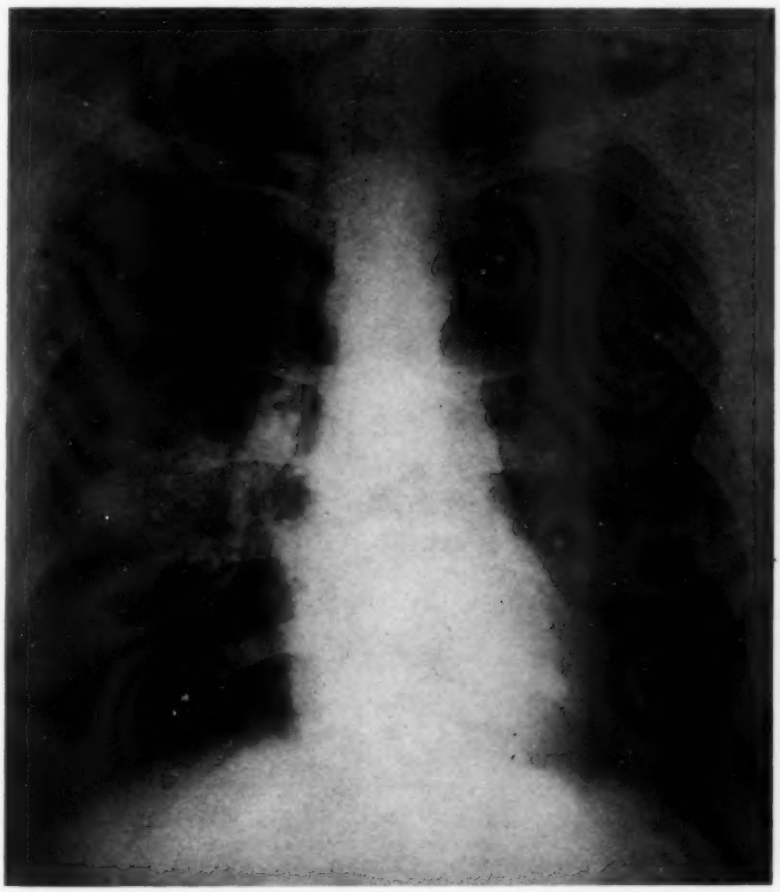

FIG. 1. *Case 5, 26* year old white male. Four day prodromal symptoms, predominately systemic. Six days of fever in hospital, maximum 103.6° F. White count 7400, polymorphonuclears 64 per cent. Fourteen days in the hospital.

demonstrate known pathogens by any laboratory method and the peculiar pathological changes in the lung with mononuclear alveolar exudate (Longcope [6]).

Pathology. The pathological picture is that of a patchy, hemorrhagic, interstitial bronchopneumonia associated with acute bronchitis and bronchiolitis. The alveolar exudate contains chiefly mononuclear cells and may

be hemorrhagic or organized. The alveolar walls are often thickened and infiltrated with mononuclears. The inflamed trachea and bronchi, on the other hand, show polymorphonuclear infiltration. Necrosis and infiltration of the wall of the pulmonary artery and its small radicles have been observed.[7] Pathologically the disease is quite similar to epidemic influenza, psittacosis, and the pneumonias associated with measles, whooping-cough, and bacillary influenza.

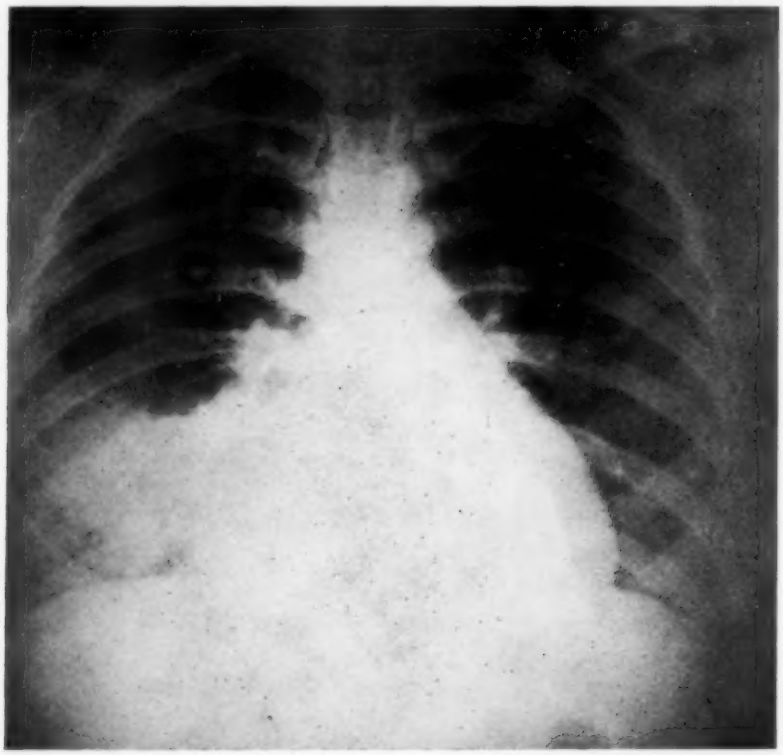

FIG. 2. *Case 8,* 28 year old staff nurse. Ill for 16 days. Fever for five days, maximum 103.8° F. White count 9,200, 82 per cent polymorphonuclears, later 15,000. Shadow remained three weeks after recovery.

Epidemiology. Evidence indicates that primary atypical pneumonia, etiology unknown, existed prior to the 1918 influenza pandemic [1] and may well have gone back beyond 1872.[1] Some have suggested that there is no current increase in the disease but that the widespread use of the roentgenogram, laboratory tests, and sulfonamide therapy have thrown it into relief.[13] Others have adduced fairly clear-cut evidence to show that the disease is increasing rapidly both in prevalence and severity.[8] Kneeland and Smetana [7] searched the records of Presbyterian Hospital (N. Y.) from 1922 through 1938. They found primary bronchopneumonia of all types to have been

extremely rare in young adults. Yet in 1940 they reported 52 cases with an average age of 31½ years. Murray [16] found a progressive increase in Harvard students from five cases in 1935–1936 to 81 cases in the 1938–1939 term. Fourteen of our cases occurred during the entire 12 months of 1941 and 23 during the first 10 months of 1942. Distribution as to sex and race is apparently equal. Little is known as to economic or occupational incidence although institutional outbreaks are common.[13, 14, 15, 16, 17] The dis-

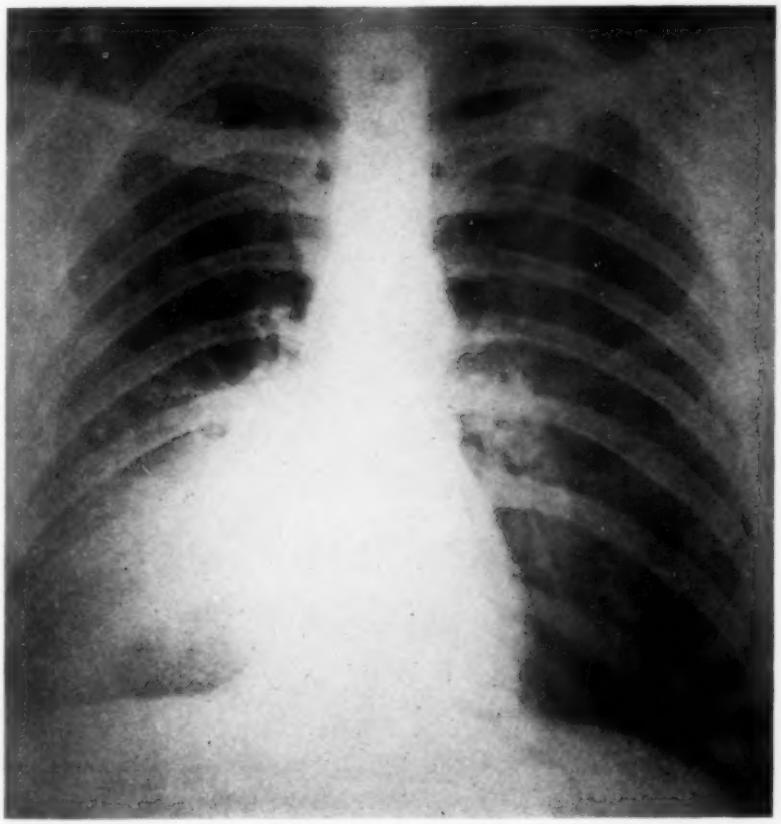

FIG. 3. *Case 10,* 21 year old white male. Six days of fever, total illness 17 days. Maximum fever 102.6° F. White count 5,600, 65 per cent polymorphonuclears.

ease occurring in contacts appears uniform in symptomatology but graded in severity.[15] Outbreaks have been reported in nearly every season and climate,[1] both with [15] and without [17] coincident epidemics of colds. The only point in the epidemiology on which there is fairly general agreement is the high incidence in young adults.

In the present group of 37 cases three were females and one was colored. Except for the latter, the proportion corresponds fairly closely with the general distribution of patients in this hospital. The mean age was 24 years.

Over half of the cases were less than 25 years old and nearly four-fifths were under 30. Only six cases were over 40. This is considerably younger than the mean age of all the patients in this hospital.

The seasonal distribution was as follows: January, 1941—one case; March, three cases; September, one case; October, four cases; November, four cases; December, one case. In January, 1942, three cases; May and June, three cases; August, two cases; September, six cases; October, nine

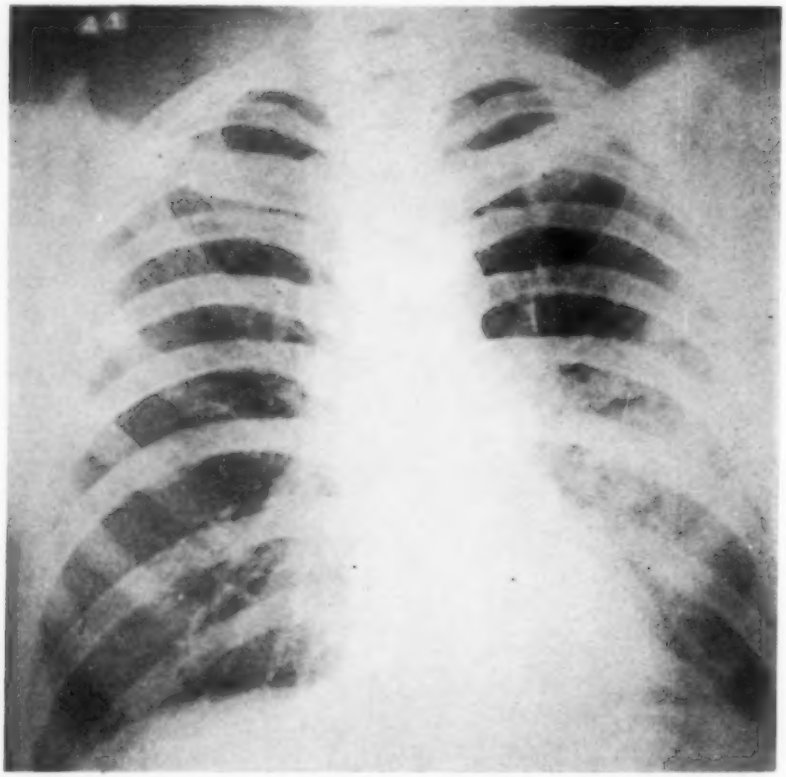

FIG. 4. *Case 11,* 24 year old white male. Sick 42 days. Relapse with chill on the twelfth day. Maximum fever 103° F. Seven sputum tests, no pneumococci. White count 8,550, 19,250, 7,300. Polymorphonuclears 65, 80 (relapse), 75 per cent. Sulfathiazole for relapse. Possible benefit.

cases. No unusual increase in the incidence of other respiratory illnesses during the two years was noted, although the incidence of atypical primary pneumonia this fall was three and a half times that of the same months of 1941.

The Average Clinical Picture. In an effort to arrive at the most representative clinical description of primary atypical pneumonia, all of the representative symptoms, signs, physical findings, clinical laboratory and roentgenographic data for each of the 37 cases were listed. The mean or the

average incidence and degree of each manifestation were determined. On the basis of these average findings the following composite, hypothetical case history was drawn up. After presenting the average clinical picture, the variables and the extremes noted in the series will be mentioned.

The Average Case. The patient was a robust Coast Guard enlisted man, aged 24 years. He entered the hospital in the fall of 1942 complaining of a "bad cold" of one week's duration. His past history indicated excellent previous health. He was vague as to any definite exposure in the previous four weeks. "Sure" he had "been

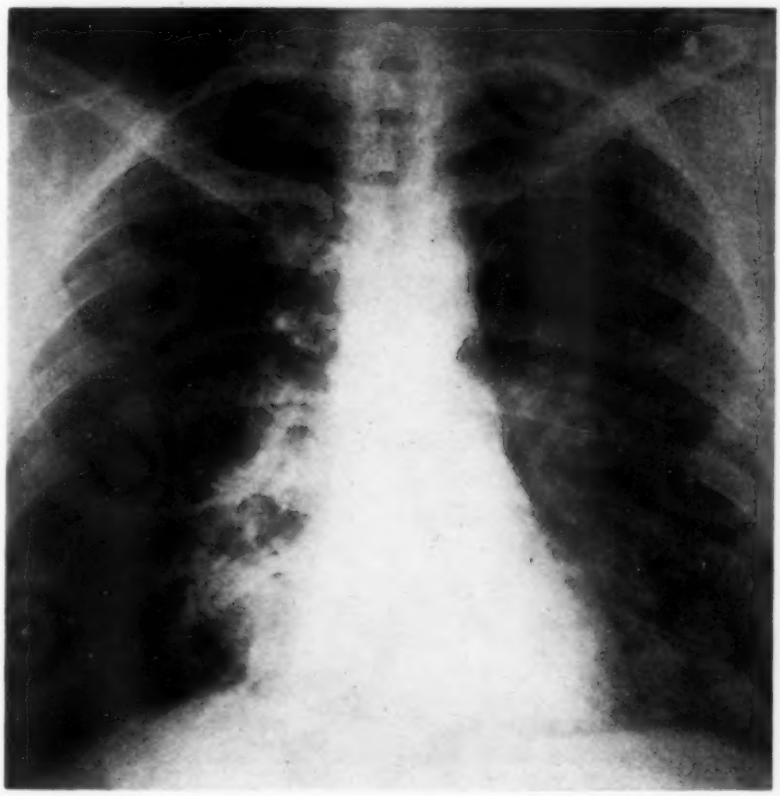

FIG. 5. *Case 27, 22* year old white male, entered hospital on third day of illness; ran fever 8 days, maximum 103.4° F., "saddle" type of fever curve. Total length of illness 24 days. White count 11,900, polymorphonuclears 87 per cent.

around people with colds, but who hasn't? None of them were very sick." His trouble started six days before he came to the hospital. At first it "didn't amount to much," just a dry tickling cough, a dry throat and perhaps a little headache. It wasn't worth reporting at first, but four days later he "really began to get sick." He had a "bad headache" all day, his throat felt raw and he coughed so much that it made his chest sore. He couldn't bring anything up except a little "phlegm." That night he "felt cold," no real shaking chills, but he just couldn't get warm. His head was splitting and he was very hoarse. During the night he had a sweat. The next morning he couldn't "turn to." He entered the sick-bay and was put to bed. That day his

throat felt better, although he was still hoarse. His cough "loosened up" a little. No, he didn't spit up any blood, "just sticky yellow stuff." He felt hot all day and his head still hurt. He couldn't eat, felt he would vomit if he did. He had a profuse sweat that afternoon and another that night. No, it didn't hurt him to breathe and he wasn't short of breath. The next morning they transferred him to the hospital. He entered the hospital on the seventh day after he caught his cold and on the third day after, as he said, he "really got sick."

Examination revealed a well-developed, well-nourished, somewhat flushed young man, who appeared uncomfortable but not gravely ill. He was rather hoarse and

FIG. 6. *Case 31,* 28 year old white male, entered on fifth day. Fever up to 102° F. Nine days of fever. Râles and roentgen-ray findings persisted for over four weeks. Had bronchial breathing on admission. White count 8,700. Shadow in right lung simulating tuberculosis.

coughed frequently, raising, with some difficulty, small amounts of mucopurulent sputum. Temperature was 101° F., pulse 92, respirations 22, blood pressure normal. The nose was not obstructed although there was a scanty, clear nasal discharge. The throat appeared moderately injected, without exudate. Examination of the chest showed slight dullness in the upper portion of the right base. Distant breath and voice sounds were heard over this area together with constant medium-moist râles. There was no tubular breathing nor pectoriloquy. Scattered elsewhere throughout the lung were occasional musical râles and rhonchi. The left lung was clear. No other abnormalities were noted.

Laboratory tests showed urine, red blood cell count, and hemoglobin to be normal. White blood cell count was 8,000 with 65 per cent polymorphonuclears. Smear and culture of the sputum showed no predominant organism and no pneumococci. There was an assortment of staphylococci, streptococci, and an occasional spirillum and fusiform bacillus. Roentgenographic report was: "In the right lower lung field, there is marked, widespread, irregular mottling with some central light clouding. Lung fields otherwise clear. Heart and great vessels normal."

Treatment consisted of bed rest, forced fluids, codeine, and other symptomatic measures. The patient did not receive sulfathiazole, but the patient in the next bed did and took just as long to get well.

On the first night the patient's temperature rose to 103° F., with pulse 108 and respirations 24. This was his maximum fever. He ran a fever for six days. A line connecting the maximum for each day would show a fairly uniform downward gradient, but the whole chart was marred by brief, very irregularly spaced dips. As the maximum daily temperature declined, more and more of these irregular dips transected the normal line. Midway in his febrile course, he was found to have a white cell count of 13,000, with 81 per cent polymorphonuclears and 6 nonsegmented cells.

The clinical symptoms cleared extremely rapidly and the patient was asking to be allowed out of bed before the fever subsided. The physical signs were slow to improve, however. Râles grew coarser, but persisted many days after he became afebrile. The roentgenogram showed only partial clearing several days after the temperature became normal. Once out of bed the patient appeared rather shaky, but professed himself well and wanted his discharge. He was retained in the hospital until roentgenographic examination on the seventeenth day showed complete clearing of the pneumonia.

Discussion

Although the hypothetical case just described represents the average of the group, it would be impossible to diagnose or treat many cases without a knowledge of the extremes as well as the means. Familiarity with the allowable variations and the possible complications is essential. The variation in the present group may be tabulated as follows (after Kneeland and Smetana):

(1) *The prodromal cold.*

No. Cases	Duration of Colds before Acute Illness
5	None
12	1–2 days
22	Less than 1 week
10	Over 1 week

This is a point on which there is much disagreement in the literature. Some series report no prodromes whatever.[17] Others stress the antecedent cold.[4, 15]

(2) *Onset.* This is practically never as severe as in lobar pneumonia. Only one case had pleuritic pain, although many complained of substernal soreness. Three cases began with chills. Two cases had slightly blood-streaked sputum. None had frankly bloody or "prune juice" sputum. All writers are in substantial agreement on these points.

(3) *Day of acute illness on arrival in hospital.* The mean day of acute illness on arrival in hospital was the third day (Kneeland and Smetana[7]

reported the fourth day). A third of the cases arrived on the day illness became acute. All but two were hospitalized in the first week.

(4) *Temperature.* The highest temperature was usually noted on the first or second day in the hospital. Many fevers were irregular. The maximum temperature ranged from 100° to 105.2° F. Average maximum was 102 to 103° F. The mean duration of the fever was six days. The range was:

Days of Fever	No. of Cases
Less than 4	13
4 to 7	9
8 to 14	11
15 to 28	4

Seven patients showed abrupt defervescence from a moderately high level. In all of these cases the duration of the febrile period was short. Another variation from the average pattern described above was the "saddle" curve observed in a few cases. Isolated brief elevations one to four days after defervescence were common. Three cases had relapses, usually during the second week. In one case relapse was ushered in by a severe chill. The fever characterizing relapses was extremely irregular.

(5) *Pulse and respiration.* There were no striking examples of bradycardia during fever although this has often been described,[8] together with relative tachycardia later in the illness. The pulse rate usually corresponded to the temperature level. The average peak was 100 to 110 per minute. Three cases had maximum heart rates in the eighties; six showed pulse rates over 120.

Although intense cyanosis is said to be a characteristic of severe cases,[7] it was noted in but two cases.

Dyspnea was uncommon. One case had a respiratory rate of 32, with asthmatic features. The mean of the maximum rates was 22.

(6) *Sore throat* has been stressed as an important early symptom.[1, 7, 8, 15] Most cases showed some pharyngeal injection. However, soreness was severe enough to cause complaints in but 10 of our cases. In six of these cases, it was a transient, early manifestation. In one case, it was absent until late. In two cases, it was present both early and late.

(7) *Hoarseness,* described as a prominent symptom, was present in nine cases (mild in five, moderate in one, and severe in three).

(8) *Paroxysmal cough* was present in all but two cases. It was extreme in 12 cases, severe in 11, and no worse than that of an average cold in 12 cases.

(9) *Severe headache* has been stressed as an important early symptom.[6, 7, 8] It was present in 18 cases and extreme in seven. It was frontal, occipital, or bitemporal, never hemicranial.

(10) *Physical signs.* Much emphasis has been laid on the absence or scarcity of physical signs as an important point in differentiating primary

atypical pneumonia from pneumococcal pneumonias.[8] In the experience of the writer this is true only insofar as signs of frank consolidation usually were absent. The extent of the lesion disclosed by roentgenogram was greater than that anticipated on physical examination. In 29 cases the site of involvement was picked up on physical examination. One case simulated frank, lobar pneumonia. Three had tubular breathing (15 per cent is the reported incidence [16]). All of these cases were seen recently. It may be that the virulence is increasing.

Râles were nearly always present, usually medium and moist in character. They became coarse during resolution. Scattered asthmatoid wheezes were heard in many cases.

Next to râles, mild to moderate dullness and suppression of breath and voice sounds were encountered. Pectoriloquy was unusual.

Transient enlargement of the spleen was encountered twice. One case had an erythematous rash.

(11) *Sputum* was almost invariably mucopurulent. Two cases showed bloodstreaking. Out of a total of 30 smears and several cultures, pneumococci were reported in but three. These were scanty and did not react to the usual typing sera. It has been noted elsewhere [6] that when pneumococci are present they almost invariably belong to the high-number groups. Organisms commonly found are *Streptococcus viridans,* staphylococci, and *Micrococcus catarrhalis.*[8]

(12) *Blood count.* Red blood cell count and hemoglobin usually were normal. White blood cell counts were taken usually on the day following admission. Average white blood cell count was 9,000. None exceeded 14,700. Mean white blood cell count ranged between 8,000 and 9,000. Differential count often was normal; it usually showed polymorphonuclears to be between 60 per cent and 80 per cent (4/5 of our cases). No case showed more than 89 per cent polymorphonuclears on admission. Many cases showed a rising white blood cell level later in disease. The maximum observed was 19,250 with 84 per cent polymorphonuclears in case 11, who had chill and relapse on the twelfth day of hospitalization. The usual peak was 12,000 to 14,000, and polymorphonuclears were proportionate.

(13) *Blood cultures* were done in about a fourth of the cases. All were sterile.

(14) *Urine.* Transient albuminuria was present in two cases. Hyalin casts were found in a small number. There were granular casts in two cases.

Mild hematuria appeared in two cases. One case showed transient findings of acute nephritis with complete recovery.

(15) Guinea pigs inoculated from case 1 were studied by Dyer for Q-fever with negative results.

(16) *Complications* in our cases were as rare as reported by others.

One case had brief nephritic manifestations. Some writers believe that resistance to pyogenic organisms increases in atypical primary pneumonia.[7, 8]

Severity	Number of Cases	Average Length of Illness
Mild	18	14 days
Moderate	14	22 days
Severe	5	34 days

(17) The longest mild case 25 days, the longest moderate case 31 days, and the longest severe case 42 days.

(18) *The length of hospitalization* often was prolonged beyond symptomatic recovery because of the inadvisability of returning the patient to duty until the roentgenogram showed complete clearing. The mean period of hospitalization was two to three weeks, with the following distribution:

Period of Hospitalization	No. of Cases
Less than 1 week	1
1 to 2 weeks	14
2 to 3 weeks	11
3 to 4 weeks	7
4 to 5 weeks	2
5 to 6 weeks	1

(19) *Mortality:* There were no deaths. The reported figure is 1 per cent.[8]

The Roentgenological Characteristics. The roentgenographic findings in primary atypical pneumonia are not pathognomonic.[7] The shadows are easily mistaken for tuberculosis or those of almost any type of pneumonia. To rule out the former it is imperative to demonstrate complete clearing of the lesion before dismissing the patient. Migrating shadows are of diagnostic value but are infrequent. They were encountered in three of the present cases. Extremely dense shadows are rare. Hilar involvement, with radiating parenchymal lesions, is common. Any portion of the lungs may be involved. Shadows vary in size and differ in character from patchy to diffuse to mixed. Rarely does the density occupy an entire lobe. Often it occupies portions of adjoining lobes.

In the present series the shadow of the lesions covered an area averaging one-sixth of that of the shadow of one lung. The types and location of lesions encountered were as follows:

	Hilar	Lower Half of Field	Upper Half	Both Lungs	Patchy	Confluent
Number	20	29	8	9	25	24

Kornblum and Reimann [4] would include cases of acute tracheobronchitis. In the 37 cases reported here diagnosis has been restricted to cases showing unmistakable parenchymal densities. It was felt that the criteria for diagnosing tracheobronchitis by roentgenogram are subject to too much confusion to justify the making of such a diagnosis by the average physician.

Treatment. Treatment is purely symptomatic.[1] Bed rest is essential. Fluids should be forced. Codeine, throat irrigations, expectorants and sedatives are welcome where indicated. Severe cases may require oxygen. Because of the sweating which characterizes the disease, diaphoretic drugs should be avoided. It is well to recognize the fact that many patients will feel weak and listless for days after clinical recovery.

Most writers agree that sulfonamide drugs are of no value. Because of the close resemblance of some cases to pneumococcal pneumonia, it will be necessary to start them on a sulfonamide drug pending the results of laboratory tests to rule out those pneumonias amenable to chemotherapy. Eleven cases received sulfathiazole and one case sulfapyridine. Nine of these showed no benefit. Three cases became afebrile after a day or two. One of the three received the drug at the time of a "relapse." The other two were mild cases and the improvement probably was coincidental. Lowell[9] recommends that chemotherapy be instituted upon the appearance of one or more of the following findings, which he believes indicative of secondary invasion by pyogenic bacteria:

(1) Increasing numbers of pathogenic organisms in the sputum.
(2) The development of bacteremia.
(3) An abrupt rise in the leukocyte count.
(4) Shaking chills.

Summary

1. The possible etiology, pathology, and epidemiology of primary atypical pneumonia, etiology undetermined, were briefly discussed.

2. A hypothetical case report based on the calculated average findings in 37 original cases was presented to illustrate the representative clinical picture.

3. The extremes and variations in the clinical and laboratory data of the original cases were presented and compared with those reported by others.

4. The roentgenological characteristics were presented and discussed.

5. The treatment was outlined.

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THE CAUSES OF DEATH IN THIRTY CASES OF RHEUMATOID ARTHRITIS *

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Rheumatoid arthritis is not just a disease of joints. It is a systemic disease characterized by manifold physiologic alterations and often by multiple symptoms. Despite its systemic nature, rheumatoid arthritis seldom causes death. A commonly held opinion is that patients who have rheumatoid arthritis rarely die of the disease. Many thousands of patients with rheumatoid arthritis have been examined at the Mayo Clinic during the past 25 years, but during this time necropsy has been performed in only 30 cases of rheumatoid arthritis. Although this number is small, we have considered it important to study the manner of death in these cases because data on the cause of death in rheumatoid arthritis are indeed meager.

Material

Our series comprises all the cases of rheumatoid arthritis in which necropsy has been performed at the clinic. Criteria for the diagnosis of rheumatoid arthritis were as follows: In each instance the arthritis had run a chronic progressive course for months or years, during which some degree of articular crippling had developed. In a few instances the arthritic process had become inactive but in each the disease had caused changes in joints which could be detected easily on clinical examination. Thus, many joints were spindle-shaped because of swelling of the joint and atrophy of juxta-articular muscles. It was common to see synovial thickening and effusions. Some degree of fibrous ankylosis was usually present. In 22 of the 25 cases in which they were made, roentgenograms disclosed the characteristic findings of rheumatoid arthritis including swelling of the soft parts, atrophy of the epiphyses, varying degrees of destruction of cartilage and narrowing of the articular spaces. In some cases marginal lippings were noted. In three of the cases significant roentgenologic changes were absent but objective and other clinical evidences (increased sedimentation rate and so forth) of rheumatoid arthritis were present. The characteristic systemic disturbances of rheumatoid arthritis, including loss of weight, secondary anemia, and increase of the sedimentation rate, were common in this series.

We wish to emphasize that we were not dealing with the so-called secondary progressive polyarthritis which is said to result from rheumatic fever. Only two of the 30 patients of this series gave a history of rheumatic fever preceding the onset of the rheumatoid arthritis: the remaining 28 did not

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present a history which suggested either rheumatic fever or any of the other so-called rheumatic equivalents, such as chorea, growing pains or erythema nodosum.

The patients varied in age from nine to 77 years at the time of their deaths. The majority were in the third to the sixth decade inclusive. The distribution of the ages by decades was as follows: first decade, one case; second decade, two cases; third decade, four; fourth decade, five; fifth decade, nine; sixth decade, six; seventh decade, two; and eighth decade, one.

Sex Ratio. Although the incidence of rheumatoid arthritis is two or three times greater among women than men, 17 of our patients were men, and only 13 were women. This reflects in part at least, the fact that the

TABLE I

Cause of Death in Thirty Cases of Rheumatoid Arthritis

Cause of Death	Cases
Cardiac disease (9 cases)	
Rheumatic cardiac disease	7
Nonrheumatic cardiac disease	2
Renal disease (3 cases)	
Acute pyelonephritis with oliguria	2
Renal amyloidosis	1
Pulmonary disease (11 cases)	
Chronic bronchiectasis with pulmonary suppuration	2
Pulmonary embolism	3
Bronchopneumonia	3
Pulmonary fat embolism	2
Postoperative massive collapse	1
Intestinal disease (2 cases)	
Chronic diarrhea of undetermined origin	2
Miscellaneous causes (5 cases)	
Cinchophen hepatitis	1
Violent accidental death	1
Carcinoma of prostate with metastasis	1
Sudden unexplained death	1
Cause of death unknown	1
Total	30

preponderance of postmortem examinations at the Mayo Clinic are performed on men. During the past five years the ratio of men to women encountered at necropsy has been 62 : 38.

The duration of the arthritis at the time of death was less than one year in four cases, between one and five years in 11 cases, and between five and 48 years in the remaining 15 cases.

In the following discussion the patients have been grouped according to the organ most obviously concerned during the terminal illness. It must be noted, however, that necropsy frequently revealed serious lesions in more than one vital organ so that an unequivocal decision as to the exact immediate cause of the patient's death has not always been possible. The causes of death are indicated in table 1.

Cardiac Deaths

Details of the cardiac lesions encountered in 25 cases of rheumatoid arthritis were reported recently.[1] Since that report appeared we have added five more cases to make the present total of 30 cases.

We have found significant although not necessarily fatal cardiac lesions in 24 of the 30 cases. In six, the heart was normal at necropsy.

Cardiac lesions in this series were as follows: Lesions indistinguishable from those of rheumatic heart disease were present in 16 of the cases. We judged the rheumatic heart disease to be the cause of the patient's death in seven of these 16 cases. In three of these seven fatal cases death was preceded by periods of congestive heart failure with anasarca, whereas in four, death was not preceded by congestive heart failure.

Other forms of cardiac disease caused two deaths as follows: one from coronary occlusion with myocardial infarction, and one from myocardial degeneration and edema of an unknown cause.

One instance of each of the following forms of heart disease were encountered but were not fatal: coronary sclerosis with chronic infarction of the myocardium; nonspecific subacute pericarditis; hypertrophy of the heart resulting from hypertension; hydropericardium; obliterative pericarditis of an unknown cause and calcareous aortic stenosis.

Deaths from Rheumatic Heart Disease with Congestive Failure. Three patients in whom this manner of death prevailed were found at necropsy to have severe deformities of the heart valves resulting in serious mechanical dysfunction.

Case Reports

Case 1. The patient, a man aged 45 years, was found to have rheumatic heart disease 16 years before his death and several months before the onset of his rheumatoid arthritis. He did not give any history of rheumatic fever, chorea, growing pains or erythema nodosum. The arthritis was confined to his spinal column and was continuously active and progressive from the time of its onset until he died. The cardiac lesion also had progressed slowly through the years, but myocardial function continued to be adequate until six weeks before he died, when progressive congestive failure with anasarca appeared and proved fatal. Necropsy disclosed chronic mitral and aortic endocarditis with dilatation of the ventricles.

Case 2. The patient, a woman aged 57 years, had suffered from a progressive form of rheumatoid arthritis for 12 years before her death. She did not give a history of rheumatic fever. Symptoms of myocardial insufficiency appeared six years before her death when she complained of shortness of breath on exertion. Subsequently crippling caused by the arthritis resulted in almost complete helplessness and inactivity. Congestive heart failure with anasarca caused her death and necropsy disclosed chronic rheumatic mitral and aortic endocarditis and pericarditis.

Case 3. The patient, a woman aged 49 years, had had rheumatoid arthritis for nine years before her death. Enlargement of the heart and irregularity of its rhythm had been discovered three years before her death. She did not give a history of rheumatic fever. The arthritis was active and progressive during these nine years, but the interphalangeal joints, one ankle and one wrist only were involved.

During convalescence from cholecystectomy signs of congestive heart failure appeared. Her condition then was complicated by signs of bronchopneumonia, pulmonary infarction and intense albuminuria.

Necropsy disclosed severe chronic rheumatic endocarditis with mitral stenosis. A number of emboli had caused pulmonary infarcts with subsequent infection of the infarcted lung. A dissecting aneurysm had formed in the right renal artery with resulting thrombosis of this vessel and infarction of the kidney.

Death from Rheumatic Carditis without Congestive Failure. Four patients died from active subacute or chronic rheumatic carditis without prominent symptoms of pulmonary or systemic edema. The alterations of the cardiac valves were not such as to interfere seriously with mechanical functioning of the heart. Heart failure had apparently resulted from active rheumatic inflammation in every case. In all cases rheumatic myocarditis was present, in three, rheumatic valvulitis, in two, rheumatic coronary arteritis, and in one, rheumatic pericarditis.

These four patients (cases 4 to 7) all had extensive rheumatoid arthritis and all died within a relatively short time after the onset of the rheumatoid arthritis. Two died in two years, a third in six years and the fourth in seven years after the onset of the rheumatoid arthritis. All displayed marked constitutional reactions including emaciation and secondary anemia together with marked weakness. All of the patients were confined to their beds or to wheel chairs for months or years before death because crippling was so severe. None recalled any history of independent episodes of rheumatic fever, yet all had active and progressive rheumatic heart disease responsible for failure of the heart.

Case 4. The patient was a girl aged 14 whose arthritis had been present only two years, but had been a rapidly progressive and a seriously crippling process. The deformities had become so extensive that she was confined to a wheel chair or to her bed. Multiple flexion contractures had appeared. A loud systolic murmur had been detected over the precordium but the physical findings were not sufficiently clear to permit the clinical diagnosis of rheumatic heart disease. She did not relate a history of rheumatic fever.

In an attempt to relieve her deformities the joints were manipulated under anesthesia by an orthopedic surgeon. During the immediate postoperative days her temperature and pulse rate increased progressively. She became rapidly weaker and died four days after the manipulations. At necropsy the heart showed chronic active rheumatic mitral endocarditis and myocarditis with chronic aortic and tricuspid endocarditis. There was no evidence of fat embolism.

Case 5. A youth aged 17 years had arthritis of six years' duration which had caused severe crippling. He did not recall any attacks of rheumatic fever. A systolic murmur could be heard over the heart, but the physical findings did not permit a conclusive clinical diagnosis of rheumatic fever. His death followed a period of increasing weakness. During the last weeks of life the heart's action was irregular.

Necropsy disclosed subacute rheumatic pericarditis, rheumatic aortitis and dilatation, grade 3, of the left ventricle, fatty degeneration of the myocardium and amyloidosis of spleen and lymph nodes.

Case 6. The patient was a woman aged 24 years whose arthritis had been present two years. During this time she had become markedly emaciated and so crippled

that she was confined to her bed. She did not give a history of rheumatic fever, but clinical evidence of enlargement of the heart indicated cardiac damage. The cause of the heart disease could not be established during life. The fatal illness was characterized by a notable exacerbation of the arthritis accompanied by tachycardia and fever. Death occurred 10 weeks after onset of this acute phase. Necropsy disclosed subacute rheumatic mitral endocarditis and myocarditis.

Case 7. The patient was a man aged 55 years whose death occurred seven years after the onset of rheumatoid arthritis. The disease had brought about an extreme grade of crippling with extensive deformities and contractures. Like the other patients of this group he did not give a history of previous rheumatic fever. The attending clinicians did not find any signs of heart disease. Death occurred suddenly after a series of convulsions of unknown origin. At necropsy rheumatic myocarditis with subacute rheumatic mitral and aortic valvulitis and rheumatic coronary arteritis were found. Nothing abnormal was found in the brain to account for the convulsions.

Other Cardiac Deaths. Two additional deaths in our series were attributable to heart disease which was not of rheumatic origin.

Case 8. The patient was a woman aged 52 years who had become a helpless invalid because of active progressive rheumatoid arthritis. This patient died suddenly from thrombosis of a coronary artery with subsequent infarction of the myocardium.

Case 9. The second death was mysterious and is as yet unexplained. The patient, a child aged nine years, had suffered from rheumatoid arthritis for 18 months. The arthritis, which was moderately severe and slowly progressive, had resulted in partial ankylosis of the hips and knees. Death occurred suddenly after a violent illness lasting nine days, during which the child had high fever and signs of dilatation of the heart. Necropsy disclosed myocardial edema and degeneration together with an inflammatory lesion of the mitral valve. This inflammatory lesion was not definitely characteristic of rheumatic fever.

Comment on the High Incidence of Rheumatic Heart Disease among Patients with Rheumatoid Arthritis

The diagnosis of rheumatic heart disease was based on the finding of varying combinations of gross and histologic lesions in the hearts. The gross lesions included diffuse thickening of the leaflets of the valves, shortening and thickening of chordae tendineae, vascularization of leaflets of the valves, varying degrees of stenosis of valves, adhesions between leaflets of valves and pericarditis. The histologic lesions included varying combinations of typical Aschoff bodies, fibrinoid degeneration of fibrous tissue, presence of proliferating basophilic histiocytes, fibrinous pericarditis, coronary arteritis, hyalinization of the stroma of valves, vascularization of leaflets of the valves, vascularization and inflammation of rings of the valves, nonbacterial verrucae on valves or mural endocardium and perivascular onion skin scars in the myocardium.

We have considered three possible explanations for the unexpected high coincidence of rheumatic heart disease and rheumatoid arthritis. The first is that we have by chance been presented with a series of cases in which an

independent, rheumatic heart disease was unusually common. If this explanation be correct, the findings in our cases do not reflect accurately the true coincidence of the two conditions. A second possibility is that the "rheumatic" cardiac lesions were not caused by rheumatic fever, but represented a similar disease caused by the agent responsible for rheumatoid arthritis. If this is correct, we observed a heretofore unrecognized condition, "rheumatoid heart disease." A third possible explanation is that rheumatoid arthritis and rheumatic fever are related and that rheumatic heart disease is commonly present in rheumatoid arthritis even in the absence of a history of frank attacks of rheumatic fever.

The first of these explanations appears to us least likely to prove correct because the cases constituting this series were chosen without regard for the presence or absence of heart disease. The presence of rheumatic heart disease, however, may increase the chance that death would occur under circumstances which would permit us to perform the necropsies.

The possibility that rheumatoid arthritis may be associated with inflammatory cardiac lesions similar in appearance but of different cause than rheumatic fever cannot be lightly dismissed. We believe, however, that the lesions which were designated by us as those of rheumatic heart disease would be so diagnosed by most American pathologists. Dr. H. E. Robertson has kindly reviewed the cardiac material and has concurred in the diagnoses of rheumatic heart disease. Dr. B. J. Clawson [2] of the University of Minnesota has likewise stated that these lesions represented rheumatic heart disease. It is interesting in this connection that in two cases, cardiac lesions were observed which were histologically strikingly similar to the subcutaneous nodules of rheumatoid arthritis. These unusual cardiac lesions have been discussed in greater detail in another report.[3]

The third possibility, that the two diseases, rheumatic fever and rheumatoid arthritis are related, is strongly suggested by our data. If this explanation is correct, however, we are at loss to explain why rheumatic heart disease is only exceptionally found among living persons with rheumatoid arthritis. Our own interest in the coincidence of the two conditions has been heightened by the experience of this study. In consequence we have since made especially careful observations of the clinical and electrocardiographic condition of the heart in a considerable number of cases of rheumatoid arthritis in our wards but we have only occasionally detected rheumatic heart disease. We are aware, of course, that clinicians are often unable to detect the presence of rheumatic heart disease during life, but the discrepancy between our clinical and postmortem experience has been extraordinarily great and we continue to be puzzled by this inconsistency.

Garrod [4] once stated that if a patient who has rheumatoid arthritis has valvular insufficiencies of the heart, it can be assumed that he had a previous unrelated attack of rheumatic fever. On this basis, the incidence of rheumatic heart disease among rheumatoid patients should be no higher than in any other group of the population. The medical literature, however, does

not reveal evidence that this question has been settled. Clinical studies are not sufficiently reliable. We know that rheumatic cardiac lesions cannot be detected on clinical examination unless they are extensive enough to produce murmurs, alterations of cardiac contours, disturbances of rhythm or electrocardiographic abnormalities. For the most part those who have made such clinical studies have not found rheumatic heart disease in an impressively large percentage of cases of rheumatoid arthritis. Thus, Dawson and Tyson [5] found mitral stenosis by clinical examinations in only seven of 100 cases of atrophic arthritis, and Monroe [6] found "valvular heart disease" on clinical examinations in only 4 per cent of 267 cases of atrophic arthritis. Master and Jaffe [7] noted that electrocardiograms gave evidence of heart disease in 100 per cent of cases of rheumatic fever, but not in any instances of acute rheumatoid arthritis.

Earlier works [8, 9, 10, 11] might be cited, but these often were marked by confusion of nomenclature or by absence of observations at necropsy. We, therefore, considered them of uncertain value.

Andrus [12] recently reported that rheumatic heart disease was present in eight of 25 cases of rheumatoid arthritis in which he performed necropsy. This incidence (32 per cent) is less than in our series but far higher than would be expected in the general population of Minneapolis where his study was conducted. His report suggests, therefore, that our observations will be substantiated if studies are carried out in other centers.

Renal Deaths

Death Caused by Acute Pyelonephritis with Oliguria. Included in this series are two cases (cases 10 and 11) in which death resulted from acute pyelonephritis and oliguria following typhoid vaccine therapy. Both cases have previously been reported in detail by one of us (Hench [13]).

Case 10. The patient was a man aged 51 years, whose arthritis had been present only three months. The articular disease was rapidly progressive and had resulted in loss of 30 pounds (13.6 kg.) and crippling which was severe enough to require the use of crutches for walking. Oliguria appeared within 24 hours of the first injection of typhoid vaccine and persisted until his death 13 days later. An attempt to reëstablish renal function by decapsulation and renal sympathectomy was unsuccessful. At necropsy the kidneys showed acute pyelonephritis.

Case 11. The patient, a man aged 38 years, had suffered from rheumatoid arthritis for six years. Crippling was so severe that he had been confined to his bed for a year. He was emaciated and anemic. The fatal anuria became apparent eight days after the first injection of typhoid vaccine. Necropsy disclosed diffuse acute pyelonephritis. Although the patient had not given a history of rheumatic fever, examination of the heart revealed healed rheumatic mitral endocarditis and myocarditis.

We do not know of any explanation for appearance of severe pyelonephritis following typhoid vaccine therapy. In neither case was evidence of pyelonephritis present before administration of typhoid vaccine. In case 10 the patient had lost 30 pounds (13.6 kg.) in three months, and in case

11 emaciation and anemia were of advanced degree. We now believe such exhausted patients are in a fragile state of health, and though they may live long with proper care, they may react with violence to certain therapeutic measures. Such patients are usually anxious to submit to any form of therapy even if it holds but slight hope of improvement. Results of therapy by typhoid vaccine shocks, however, have not led us to believe severely crippled patients can be significantly improved thereby, and we now regard extensive crippling, severe emaciation and severe anemia to be contraindications to typhoid vaccine therapy in rheumatoid arthritis.

The risk from foreign protein therapy with typhoid vaccine is apparently slight but definite. By 1932, one of us (Hench) had observed three deaths among 2,500 patients so treated. The mortality rate from this form of treatment was estimated to be 0.12 per cent. Since this report, which drew attention to contraindications and need for care in selecting candidates for typhoid vaccine therapy, only one death has been observed among patients treated by this method at the clinic. The relative safety of this form of treatment was stressed by Cecil [14] in 1935, who said he had never seen a death or an untoward reaction in a case of arthritis treated with typhoid vaccine, and by Tucker [15] who stated in 1938 that no deaths had occurred among several hundred patients treated with typhoid vaccine at the Cleveland Clinic.

Death Caused by Renal Amyloidosis. Severe amyloidosis with extensive involvement of the kidneys resulted in the death of one patient (case 12). A lesser degree of amyloidosis without serious renal involvement was found in an additional case (case 5), making the incidence of amyloidosis 6.6 per cent in our series.

Case 12. The patient whose death resulted from renal amyloidosis was a man aged 48 years. Rheumatoid arthritis had been present six years. The arthritis which was of wide extension affected shoulders, elbows, wrists, hands, hips, knees and feet. The patient was emaciated, weak and crippled. The clinical phenomena which should attract attention to the possibility of amyloidosis were characteristically present. These included symptoms of nephrosis, albuminuria, edema and reduced renal function, together with palpable enlargement of the lymph nodes, liver and spleen. The blood pressure was so low (60 to 108 mm. of mercury systolic, 40 to 76 diastolic) that suprarenal insufficiency was suspected during life and confirmed by discovery of severe amyloid degeneration of the suprarenal glands at necropsy. The concentration of albumin was lowered to 1.1 gm., and that of the globulin to 2.6 gm. per 100 c.c. of serum; the albumin-globulin ratio was inverted, 1 : 2.3, and the concentration of cholesterol was high (268 to 315 mg. per 100 c.c. of serum). Curiously, a congo red test for amyloid gave negative results.

The patient did not relate any history of attacks of rheumatic fever but necropsy revealed chronic active rheumatic mitral endocarditis with a noninfected thrombus attached to the leaflets of the valves. Acute and chronic rheumatic aortitis also were noted together with localized foci of rheumatic myocarditis and amyloid degeneration of the kidneys, suprarenal glands, spleen, liver and esophagus.

Several possible explanations can be offered for the relation of rheumatoid arthritis and amyloid degeneration but none is well established. Experiments have indicated some connection between hyperglobulinemia and

amyloidosis but whether hyperglobulinemia causes amyloid degeneration is uncertain. Ecklund and Reimann [16] induced in rabbits hyperglobulinemia by repeated injections of sodium caseinate and noted that it regularly preceded the development of amyloidosis. Letterer [17] claimed to have shown that hyperglobulinemia alone is not sufficient to cause amyloidosis, but must be associated with exhaustion of immunity resources. He pointed out that this might be expected after a long illness. An increase of the globulin in the blood serum has been observed frequently in some, but not in all cases of rheumatoid [18, 19, 20] arthritis. Perhaps, therefore, hyperglobulinemia and the long exhausting illness of rheumatoid arthritis may have been factors in causing amyloidosis to appear in our two cases.

A further possible cause of the amyloidosis was suggested by Reimann and Ecklund [21] who reported one case of fatal amyloidosis complicating rheumatoid arthritis which had been treated extensively with vaccines. These authors attributed the amyloidosis to vaccine therapy. Our patients likewise had received vaccine therapy although the amounts are unknown. We are doubtful of the significance of this factor, however, for amyloidosis was reported as a complication of rheumatoid arthritis before introduction of vaccine therapy.

A third attitude was suggested by Moschcowitz [22] who reported two instances of coincident chronic arthritis and amyloidosis and concluded that the arthritis was not the cause of the amyloidosis, but rather that both conditions were simultaneous reactions to the same insult. Only future developments may be expected to clarify the problem.

The literature contains many additional reports of amyloid degeneration observed at necropsy in cases of rheumatoid arthritis and we have noted that nearly every study on amyloidosis refers to an occasional case associated with rheumatoid arthritis. An unusually high incidence may be noted in a paper by Portis [23] who found amyloidosis in seven of 14 cases of Still's disease reviewed by him.

Pulmonary Deaths

Deaths Caused by Chronic Bronchiectasis with Diffuse Pulmonary Suppuration. This manner of death prevailed in two cases of this series.

Case 13. The first of these patients was a woman aged 49 years who had rheumatoid arthritis of 19 years' duration. During these years, the joints had become notably deformed and many showed advanced subluxations. However, these joints had become painless and it appeared that the arthritis had reached an inactive or burned out phase. One year before her death symptoms of pulmonary suppuration developed. This condition eventually proved fatal. The arthritis and the pulmonary disease apparently were not related. This patient did not give any history of rheumatic fever and did not have any clinical signs that would permit a diagnosis of rheumatic heart disease, yet at necropsy the heart showed an acute exacerbation of chronic rheumatic pericarditis with acute focal myocarditis, coronary arteritis and mitral valvulitis.

Case 14. The second patient, who died eight months after the onset of chronic pulmonary suppuration, did not acquire rheumatoid arthritis until three months before his death. The arthritis was only moderately severe and was confined to the hands, elbows and shoulders.

Deaths Caused by Pulmonary Embolism. Our series includes three cases (cases 15, 16 and 17) in which death was the result of massive pulmonary embolism and two in which pulmonary embolism represented a contributing cause of death. Two deaths from this accident occurred after orthopedic manipulations and applications of casts; the third was unrelated to any therapeutic procedure.

Cases 15 and 16. The arthritis had been present for many years before death (30 years, case 15 and 18 years, case 16). The arthritis in both had advanced to the "orthopedic phase" with extensive deformities and contractures. These two patients were, therefore, subjected to manipulations and applications of casts. The death of one occurred 15 days after application of casts. The second patient died six days after osteotomy on the left knee and brisement forcé to the left hip, right ankle and knee. Necropsy did not reveal rheumatic heart disease in either case.

Case 17. The patient was a man 55 years of age. His arthritis which was of brief duration (nine months) was moderately severe and affected hands, wrists, elbows and knees. He required the use of crutches in walking. Pulmonary infarction occurred without relation to surgical or orthopedic procedures. His death did not result immediately after the pulmonary infarction but occurred within three months, as a result of secondary infection and suppuration of the infarcted zone of the lung. Necropsy disclosed no evidence of rheumatic heart disease.

No other similar accident occurred among our cases of rheumatoid arthritis and we cannot see any clear relation between the two conditions. During the 25 years covered by the present survey many patients who had rheumatoid arthritis have been subjected to surgical procedures at the clinic, and the fact that only two instances of fatal postoperative pulmonary embolism are included in this series permits us to conclude that the incidence of this accident is not unusually high among such patients.

Death Caused by Bronchopneumonia. Three patients died as a result of bronchopneumonia, and although bronchopneumonia is a commonplace cause of death, these patients deserve study because each acquired the bronchopneumonia in the course of therapeutic procedures directed against the arthritis.

Case 18. The first patient of this group was a woman aged 42 years, whose arthritis had been present for four years. It involved most of the peripheral joints. The arthritic process was active and progressive. Fatal bronchopneumonia appeared 48 hours following a second intravenous injection of typhoid vaccine. This patient related a history of three independent episodes of rheumatic fever and was found to have chronic rheumatic heart disease clinically and at necropsy.

Case 19. The patient, a man aged 47 years, had had rheumatoid arthritis approximately five years. It had involved the feet, the spinal column and one shoulder, and was moderately active. Fatal bronchopneumonia associated with a striking exacerbation of the arthritis appeared one week following surgical removal of infected tonsils. Neither clinical nor necropsy evidence of cardiac disease was found.

Case 20. The patient was a woman aged 24 whose rheumatoid arthritis had been present two years and had affected most of the peripheral joints. She stated that she had experienced an episode of rheumatic fever in childhood. Fatal bronchopneumonia in this instance represented a postoperative complication following cholecystectomy and did not appear in any other way related to the arthritis. Necropsy disclosed chronic rheumatic pericarditis.

The record in case 18 suggests that fatal bronchopneumonia must be anticipated as an untoward reaction to typhoid vaccine therapy, even if the general condition of the patient appears to be satisfactory. Such an occurrence, however, is exceedingly rare. No other cases of fatal bronchopneumonia complicating typhoid vaccine therapy were recorded by one of us (Hench) who in 1932 reviewed extensively the literature relating to foreign protein therapy and we could not find reports of this accident in the literature which has appeared since publication of that paper.

Death Caused by Pulmonary Fat Embolism. In our series are included two patients whose deaths resulted from pulmonary fat embolism.

Case 21. The first was a woman aged 32 years, most of whose peripheral joints were affected by the rheumatoid arthritis. This condition had been present for 11 years and had resulted in severe emaciation and marked crippling that necessitated a life in bed. Pulmonary fat embolism resulted in death, 50 minutes after orthopedic manipulations of the deformed joints. The patient did not give a history of rheumatic fever and clinical signs of rheumatic heart disease were not present. At necropsy, however, healed rheumatic mitral endocarditis and myocarditis were found.

Case 22. The patient, a woman aged 53 years, had had arthritis 23 years. She was well nourished but the arthritis was extensive and involved shoulders, elbows, wrists, hands, hips and knees. Death occurred eight hours after gentle manipulations which were carried out during the course of routine physical therapy. There was no history of rheumatic fever nor any clinical evidence of rheumatic heart disease, yet chronic rheumatic mitral endocarditis with stenosis was found at necropsy.

The condition requisite for occurrence of pulmonary fat embolism is accumulation of free fluid fat under a tension greater than venous pressure in a region where open veins are present. This circumstance may be met in a case of rheumatoid arthritis in which manipulation of joints has been performed. In the course of this disease more or less severe osteoporosis of subchondral bone appears. Lamellae of bone are absorbed and large fat-containing marrow spaces are left. The plate of subchondral bone then rests on greatly weakened metaphyseal bone which may easily be fractured by minor trauma incurred even during skillful manipulations, surgical or nonsurgical (that is, simple physical therapy).

The fat which occupies the subchondral marrow spaces in rheumatoid arthritis is plentiful. If fractures occur in the region of affected joints, fat may be released and find its way directly into the venous circulation.

When fat droplets reach the lungs, obstruction of capillaries, interference with exchange of gases and flow of blood from the right side of the heart result. In such cases a serosanguineous exudate rapidly forms in the alveoli and interferes further with exchange of gases.[24, 25] Fat droplets

may succeed in passing the lungs and then may reach the brain where they provoke necrosis of cerebral tissue adjacent to the obstructed capillaries. Some fat may reach the kidneys and be excreted in the urine.

Death may result immediately on occurrence of fat embolism, and occasionally has occurred during an operation. Usually, however, death is

TABLE II
Fat Embolism in Cases of Arthritis

Authors	Date	Cases	Operation	Age, yrs.	Diagnosis	Interval Between Operation and Death
Wahncau: Quoted by Ahrens, A.: Beitr. z. klin. Chir., 1895, xiv, 235.	1886	1	Brisement forcé	8	Polyarticular arthritis	3 days
Lympius, M.: Zentralbl. f. Chir., 1896, xxiii, 800.	1893	1	Brisement forcé	71		During operation
Ahrens, A.: Beitr. z. klin. Chir., 1895, xiv, 235.	1895	1	Brisement forcé	53	Ankylosis of knees	3 days
Eberth, J. C.: Fortschr. d. Med., 1898, xvi, 251.	1898	1	Brisement forcé	19	Chronic rheumatism	20 hours
Payr: Quoted by Warthin, A. S.: Internat. Clin., s. xxiii 1913, iv, 171.	1898	1	Brisement forcé	?	Contracture of knee	1 day
Jentzsch: Quoted by Warthin, A. S.: Internat. Clin., s. xxiii 1913, iv, 171.	1898	1	Brisement forcé	?		Not stated
Clark, B. E.: Jr. Am. Med. Assoc., 1927, lxxxviii, 919.	1927	2	Brisement forcé	37	Arthritis with flexion deformities of knees	5 hours
			Brisement forcé	?	Arthritis with flexion deformities of knees	½ hour after 4th manipulation
Kuhns, J. G. and Joplin, R. J.: New England Jr. Med., 1936, ccxv, 268.	1936	2	"Operations"	?	Atrophic arthritis	Not stated

delayed for a number of hours, occasionally for two or three days but rarely longer. Death occurred in case 20 fifty minutes after manipulation and in case 21 eight hours following manipulation.

The character of the premortem symptoms depends on whether the pulmonary or cerebral circulations have been predominantly obstructed. In the so-called pulmonary type of fat embolism (such as the two cases of our series), prominent symptoms are dyspnea, cough, cyanosis and a sense of constriction in the thorax. In the presence of predominant cerebral damage patients may become drowsy or comatose and may have tremors or convulsions. In both varieties the temperature may increase rapidly or de-

crease to subnormal levels and the blood pressure usually decreases. Frothy, blood streaked sputum containing globules of fat may be present and fat droplets may be detected in the urine. The blood count and level of hemoglobin may decrease rapidly and significantly.

Previous reports of fatal fat embolism in cases of arthritis in which the joints have been manipulated are summarized in table 2. Unquestionably many instances have not been reported.

Other reported accidents which have followed brisement forcé include rupture of the popliteal artery, rupture of the veins within the knee joint, injury to the peroneal nerve with subsequent paralysis, rupture of the skin, subluxations and fractures of the ends of the bones.

Death Caused by Postoperative Massive Collapse of the Lungs. This accident caused one death in our series.

Case 23. This man was aged 34 years. Many circumstances coöperated to interfere with his normal respiration. Severe spondylitis deformans (rheumatoid spondylitis, spondylitis rhizomelique) present for 13 years had resulted in notable restriction of expansion of the chest. The patient also had a large incisional hernia and was overweight. Respiration, already seriously impeded by the spondylitis, was embarrassed further by replacement into the abdomen of the contents of his hernia. Massive collapse of the lungs resulted. There was neither clinical nor necropsy evidence of rheumatic heart disease.

This patient's record is an isolated example but it may serve as an indication of need for some caution in planning operation on patients who have rheumatoid spondylitis.

Death from Intestinal Disease and Miscellaneous Causes

Long Continued Diarrhea of Unknown Origin. Two persons who had severe extensive deforming rheumatoid arthritis died after a long period of chronic diarrhea. Diarrhea had persisted in one case (case 24) for five months and in the second (case 25) for a year. Both patients died of exhaustion to which the diarrhea contributed largely.

Case 24. The patient was a man aged 63 years, whose rheumatoid arthritis had been present since he was 15 years of age. He presented the picture of the end stage of rheumatoid arthritis with emaciation, dry, scaly skin, almost complete helplessness resulting from deformities and confinement to bed. The arthritis was considered to be in a stage of exacerbation during the final illness. Diarrhea appeared five months before his death and persisted until death. Roentgenologic examination of the colon and bacteriologic studies of the stools made during the fatal illness failed to reveal any cause for the diarrhea. Examination of the gastrointestinal tract at necropsy revealed only insignificant ulcerations which we interpreted as probably secondary to the prolonged diarrhea. Although he did not give a history of rheumatic fever, necropsy revealed a chronic rheumatic mitral and aortic endocarditis with calcification and healed rheumatic myocarditis.

Case 25. The patient was a man aged 22 years, whose arthritis had been present only three years, but in this time had provoked extensive deformities and such severe crippling that he was confined to bed. Painless diarrhea appeared one year before

death and except for occasional intermissions, persisted until his death. The arthritis was active and progressive until death occurred. Roentgenologic studies of the colon and bacteriologic studies of the stools during life failed to reveal any cause for the diarrhea. Necropsy revealed only slight congestion of the mucous membrane of the colon. The patient did not give a history of rheumatic fever and cardiac lesions were not noted at necropsy.

Clinical examinations failed to show any lesions which could explain the diarrhea in these cases, and our examinations of the gastrointestinal tracts at necropsy likewise have failed to provide any adequate explanation for the symptom. The only lesions noted were minor intestinal inflammatory processes and slight ulcerations which we considered probably secondary to, rather than the cause of, the diarrhea. It was concluded during the life of these patients that the diarrhea was being caused by some functional disturbance of the intestine such as that which is probably present in cases of sprue or pellagra.

Periods of diarrhea were recorded in seven of the 14 fatal instances of Still's disease reviewed by Portis.[28] Stools were said to be bloody in three cases and vomiting usually was associated with the diarrhea. Portis reported the finding of a significant anatomic lesion in only one of these cases, that of a child who had ulcerative colitis.

Miscellaneous Causes. In five additional cases death resulted from coincidental or accidental causes (table 1). In one case in which only partial necropsy was performed, no data were available as to the manner of death, but it was found that this patient had rheumatic heart disease.

Comment

We have included herein all the cases which could satisfy our criteria for the diagnosis of rheumatoid arthritis in which postmortem examination had been performed at the Mayo Clinic. Our material, therefore, may be representative of rheumatoid arthritis in general but the size of the series is admittedly small. When a larger series has been studied we may see an alteration of the apparent importance of some of our observations.

Consideration of our material suggests that rheumatoid arthritis is associated with, or predisposes patients to, certain possibly fatal visceral lesions. These include rheumatic heart disease, and by all odds this was the most striking and most significant of the serious coincidental visceral diseases. Also included among these coincidental and possibly fatal defects are the functional disturbances which resulted in fatal exhausting chronic diarrhea in two of our patients. Amyloid degeneration must be considered as a further potentially fatal associated disease.

We have encountered in this series also, a noteworthy incidence of fatalities related to therapy. We consider this observation deserving of special emphasis. Even some of the minor medical and orthopedic measures which are now in daily use and which are ordinarily considered relatively harmless

proved capable of causing death. Our study indicates also that patients who have advanced and severely deforming and debilitating rheumatoid arthritis may react with unexpected violence to relatively minor therapeutic procedures. For example, typhoid vaccine therapy provoked fatal pyelonephritis and oliguria and also fatal bronchopneumonia. Cinchophen was responsible for fatal hepatitis. Operations of brisement forcé resulted in fatal fat embolism, applications of casts were followed by fatal pulmonary embolism, and herniorrhaphy resulted in the death of a spondylitic patient because of massive collapse of the lungs.

As might be expected, the series also includes a number of fatalities which cannot in any way be related to the arthritis. These included deaths as a result of carcinoma, violent accidental deaths and deaths from chronic pulmonary suppuration. We considered the coincidence of such lesions with rheumatoid arthritis to be purely accidental.

Detailed consideration of the associated necropsy findings in these cases has been recorded in a previous paper.[26] It may be noted that in addition to the pulmonary lesions already described, we frequently found terminal bronchopneumonia. Some degree of enlargement of the spleen was common. This enlargement usually had resulted from chronic passive congestion or from hyperplasia of reticulo-endothelial cells. Degeneration of splenic malpighian corpuscles was not uncommon. The most commonly encountered hepatic lesions were gross hypertrophy or atrophy, chronic passive congestion, fatty change, atrophy of the cells about central veins, central necrosis and the serous hepatitis of Rössle and Eppinger. Notable renal lesions included glomerulitis, observed in more than half of the cases, and chronic interstitial nephritis. Lesions in lymph nodes included proliferation of reticulo-endothelial cells, degeneration of secondary centers and amyloid deposits.

Because of our studies [27, 28, 29, 30, 31] on the effect of hepatitis and jaundice on rheumatoid arthritis, we had hoped perhaps to find some hitherto un-noted hepatic lesions which might be related to rheumatoid arthritis. We did find various hepatic lesions but so far have been unable to determine their significance in relation to the arthritis.

There were two surprises: (1) the relatively high incidence of cardiac lesions indistinguishable from those of rheumatic fever despite the fact that only two of 30 patients gave histories of rheumatic fever, and (2) the relative frequency of microscopic renal lesions. Clinical evidence of renal lesions is so rare in rheumatoid arthritis and so relatively common in gouty arthritis that this is a useful axiom: In cases of acute and chronic arthritis with clinical evidences of nephritis, suspect gouty, not rheumatoid arthritis.

Having found these cardiac and renal lesions at necropsy, we have gone back to our hospitalized and office patients in an attempt to find clinical evidences of cardiac or renal disease, but have been unable to find such evidence in any significant percentage. We are disturbed at this discrepancy between our clinical and our necropsy data. We are certainly not rushing to conclude

that rheumatic fever and rheumatoid arthritis are the same disease. Perhaps future study will indicate that these cardiac lesions represent rheumatoid heart disease and not rheumatic heart disease, although such a conclusion would involve a revolution in our concept concerning the specificity of lesions of rheumatic carditis.

Summary

Data regarding all cases of rheumatoid arthritis which have been observed at necropsy in the Mayo Clinic have been assembled and reviewed in order to establish the manner in which the patients died. The series comprises 30 cases. The 30 deaths in this series could be listed under three headings: (1) those which seemingly resulted from the rheumatoid arthritis itself (10 cases); (2) those which were related to treatment of the arthritis (eight cases) and (3) those from causes unrelated to the arthritis or its treatment (12 cases).

An unexpectedly high incidence of rheumatic heart disease was discovered. This condition was present in 16 of the 30 patients. It was often serious and was responsible for the deaths of seven patients. In the other nine of the 16 cases in which rheumatic heart disease was present it was not responsible for death.

Pulmonary diseases were the most common causes of death in this series. These were of varying character including pneumonia, chronic suppuration, pulmonary embolism, fat embolism and massive collapse. Renal lesions were responsible for three deaths. The lesions present in two cases were acute pyelonephritis with oliguria and in one, fatal amyloid degeneration. Prolonged diarrhea of an unknown origin was responsible for two of the deaths. In five of the 30 cases death resulted from a miscellaneous group of causes. These included cinchophen hepatitis, carcinoma and violence. In two patients, the exact manner of death is unknown.

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BACTEROIDES INFECTIONS OF THE CENTRAL NERVOUS SYSTEM *

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THIS paper describes two cases of meningitis and two cases of brain abscess caused by anaerobic, gram-negative, non-spore-bearing bacilli (genus *Bacteroides*). The portal of entry of the infection into the central nervous system in our cases and in the majority of cases in the literature was chronic suppurative otitis media. In view of this portal of entry, it is of interest to note that various species of *Bacteroides* have been described as inhabitants of the nasopharynx [1] whence the ear infection may be presumed to have arisen.

Meningitis of otitic origin is usually associated with the common, aerobic, pyogenic organisms. In a series of 231 cases, Neal, Jackson and Appelbaum [2] found streptococci in 121, pneumococci in 75, *B. influenzae* in 20, staphylococci in seven, *B. coli* in two, *B. friedländer* in two, Torula in one. Organisms designated as *Streptothrix* were recovered in three instances. These organisms were described elsewhere [3, 4] as gram-amphophilic anaerobes which exhibited branching and were designated as *Actinomyces*. Many years ago Rist [5, 6] reported a case of meningitis and two cases of brain abscess from which he isolated *Bacteroides*, and since that time a few additional case reports have appeared, references to which are given in table 1.

The observation of four cases in this hospital within the past two years would indicate that *Bacteroides* infections of the meninges and brain could be demonstrated more commonly were they sought with appropriate anaerobic cultural methods. As a rule, a satisfactory medium for the cultivation of *Bacteroides* is the ordinary meat tube, boiled to expel oxygen, then cooled, inoculated and sealed with paraffin to exclude air and maintain anaerobiosis. The addition of ascitic fluid (30 per cent) to the meat tubes, after they have been boiled and cooled, is a useful method for accelerating growth, especially on primary isolation. This action of ascitic fluid was noted in the study of the first strain of *Bacteroides* which we encountered. When the second case appeared, the spinal fluid was inoculated into two meat tubes, only one of which was enriched with ascitic fluid. The enriched tube yielded growth after 48 hours' incubation; the unenriched tube did not show growth until after two weeks' incubation. This is a point of considerable importance in

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clinical laboratories where speed in diagnosis is very desirable. Brewer's thioglycollate medium,[25] which may be enriched with ascitic fluid, has also proved very satisfactory.

Table 1 summarizes the data on 13 cases of *Bacteroides* infection of the central nervous system. In each case, the infection arose from chronic otitis which usually extended into the mastoid. At least two additional cases are on record, in one of which a brain abscess arose in a patient with bronchiectasis [7]; in the other a meningitis occurred in a patient about whom no clinical data are available.[8]

TABLE I

Bacteroides Infections of the Central Nervous System

Author	Case	Age	Days from Onset CNS Symptoms to Death or Recovery	Day of Mastoidectomy	Meningitis	Brain Abscess	Sinus Thrombosis	Lung Infarcts	Species of Bacteroides	Result
Rist[5]	X	9½	8	8th	+	0	+	+	Unidentified	Death
Rist[5]	XIII	11	9	8th	0	+	+	+	*B. ramosus* *B. serpens*	Death
Rist[5]	XV	10	4+	No op.	0	+	0	0	Espece A*	Death
Ghon et al.[9]	I	56	?	No op.	+	0	0	0	B. of Ghon[13a]	Death
Ghon et al.[10]	II	48	4	4th	+	0	+	0	Unidentified*	Death
Ghon et al.[11]	III	40	9	4th	+	0	0	0	*Spirillum nigrum*	Death
Ghon et al.[12]	IV	21	4	2nd	+	0	0	0	B. of Ghon*	Death
Freund[14]		18	8	No op.	+	0	0	0	B. of Freund*	Death
Newhart[15]		32	34	18th	+	+	+	+	*B. fragilis*	Death
Smith et al.**	1	35	79	4th	+	0	0	0	*B. funduliformis*	Recovery
Smith et al.**	2	43	9	8th	+	+	0	+	*B. funduliformis*	Death
Smith et al.**	3	50	84	2nd	+	0	0	0	*B. mucosum*	Recovery
Smith et al.**	4	37	129	5th	+	+	0	0	*B. funduliformis*	Recovery

* Organisms best regarded as members of "*B. funduliformis* group" rather than as distinct species.

** Cases reported in this paper.

CASE REPORTS

Case 1. J. U., 35 year old truck driver, had had chronic right otitis media since early childhood. Four days before admission he began to complain of frontal headache. There was no nausea or vomiting. On admission, January 9, 1941, he was severely ill, delirious, his neck was stiff, and Kernig's sign was present bilaterally. The right ear drum was perforated and a foul-smelling discharge was draining from this ear. The temperature was 103° F., the pulse 100, respirations 25. The remainder of the physical examination was not remarkable. Spinal fluid was turbid, containing 18,700 cells per cu. mm., 90 per cent of which were polymorphonuclears. There was only a trace of sugar. No organisms were seen in the smear and none grew in cultures incubated aerobically.

Operation * revealed pus in the mastoid, semicircular canals and vestibule. Sulfapyridine therapy was given as indicated in chart 1.

Spinal fluid on the following two days resembled thick yellow pus and contained many intracellular gram-negative bacilli 1 to 2 micra in length and many longer extracellular forms. These organisms grew out only in anaerobic cultures.

The patient remained febrile and semicomatose for three weeks, exhibiting marked spasticity of all extremities. He received four blood transfusions and daily intravenous infusions of saline and glucose solutions. Jaundice, with a serum van den Bergh of 9.5 mg. per cent (biphasic), was noted on the seventh hospital day.

* Operator, Dr. Edgar Holmes.

Sulfapyridine dosage was, therefore, reduced. The jaundice, which cleared within 10 days, may have been due to the drug or a transfusion reaction, but more likely to the infection since there was a marked anemia and the organism from this case was hemolytic. Jaundice is commonly seen in *Bacteroides* septicemias.[16] On the nineteenth day swelling and tenderness of the left wrist were observed. This was followed by similar involvement of the right wrist, the metacarpophalangeal joints of the right hand and both elbow joints. All these joints cleared within the next two weeks. After the thirtieth day the patient improved rapidly and was discharged well on the seventy-ninth. The only sequelae were right peripheral facial paralysis

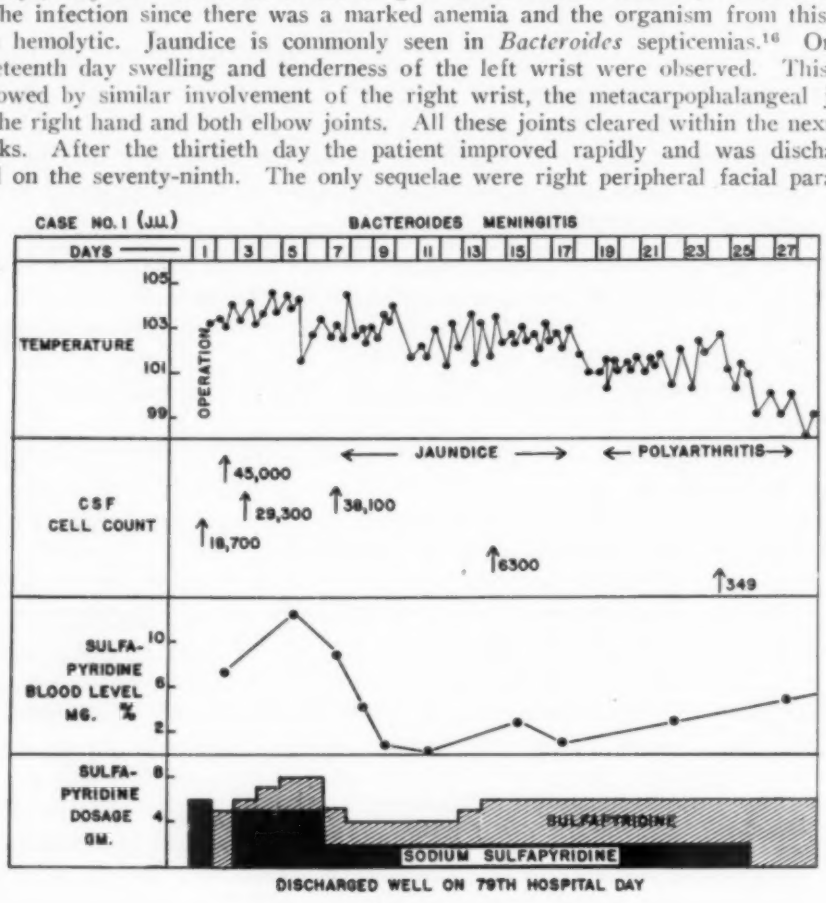

CHART 1.

and limitation of motion of the right elbow, roentgenogram of which showed calcification in the muscles over the anterior surface of the humerus.

Laboratory data. The red blood cell count fell from 4,040,000 to 2,880,000 cells per cu. mm., the hemoglobin from 91 to 57 per cent. The white blood cell count ranged between 21,100 and 12,500, polymorphonuclears comprising 92 to 88 per cent of the cells. Occasionally the urine contained albumin and white blood cells.

The cell counts of all samples of spinal fluid are given in the chart. Complete data on two samples are as follows:

Date	Pressure mm. H_2O Initial/Final	Cell Count	PMN %	Lymph. %	Sugar mg. %	Protein mg. %	Chlorides mg. %
Jan. 10	350/150	45,000	100	0	Trace	348	643
Feb. 1	125/ 80	349	80	20	129	222	644

A gold sol curve on January 9 was read 1555555332.

Bacteriology. The organisms from the spinal fluid grew out after 48 hours' incubation in meat tubes enriched with 30 per cent ascitic fluid and sealed with paraffin. The broth was diffusely turbid and 2 to 3 c.c. of gas had collected under the seal. This and all subcultures had a foul odor, and growth was never observed except under anaerobic conditions. The organisms grew slowly as a white flocculent sediment in plain infusion broth. Their growth was made rapid and diffuse by the addition of ascitic fluid or animal serum. The optimum growth temperature was 37° C., but growth did occur at 24° C.

Colonies on ascitic agar plates were smooth, yellowish gray, low convex with entire edge, easily emulsifiable, and attained a diameter of 1 mm. after 48 hours' growth. Colonies on blood agar plates were much smaller. They showed a 3 to 5 mm. zone of beta hemolysis after four or five days.

The organisms were usually seen as bacilli 1 to 4 micra in length lying singly or in end to end pairs, but they were markedly pleomorphic (figure 1). Many

FIG. 1. 24-hour thioglycollate broth culture of organism from Case 1. Note swollen and curved forms. The swellings evolve into free-lying large bodies. They are not spores. Giemsa stain. 2000 ×.

individuals were curved and exhibited a swelling at one end or near the middle. These swellings evolved into the free-lying large bodies, whose significance and relation to L type variation are described elsewhere.[17, 18] Filaments 10 to 100 micra in length were occasionally seen. The shorter forms often exhibited bipolar staining, whereas the longer filaments stained irregularly and thus had a beaded appearance. In broth, long chains resembling streptococci formed. These organisms were gram-negative and non-motile. They produced both hydrogen sulfide and indol and were killed by a temperature of 60° C. for 20 minutes. Neither spores nor capsules were observed.

Subcutaneous injection of 0.5 c.c. of culture into a guinea pig and a rabbit resulted in only a localized abscess which broke down and healed after one week. Intravenous injection into a rabbit resulted in progressive weight loss and cachexia with death after one month. No lesions could be found at autopsy. Intraperitoneal injection into a guinea pig and two adult mice was uneventful. Similar injection into

mice two weeks old resulted in death with diffuse peritonitis within 48 hours. Only transient localized inflammation developed in mice after subcutaneous injections.

This strain closely resembles organisms known as *B. funduliformis* [19] or *B. thetoides*.[6] A comparative description of these and related strains, such as the bacillus of Ghon and the bacillus of Freund, is given by Freund [14] and outlined in Bergey's Manual.[20] The problem of identification of true species within the genus *Bacteroides* is well set forth by the studies of Henthorne, Thompson and Beaver [21] and Lewis and Rettger [22] on strains of intestinal origin. We would favor the view that strains exhibiting the curious pleomorphism described above are best regarded as members of a "*B. funduliformis* group" until such time as adequate criteria for exact species differentiation are at hand.

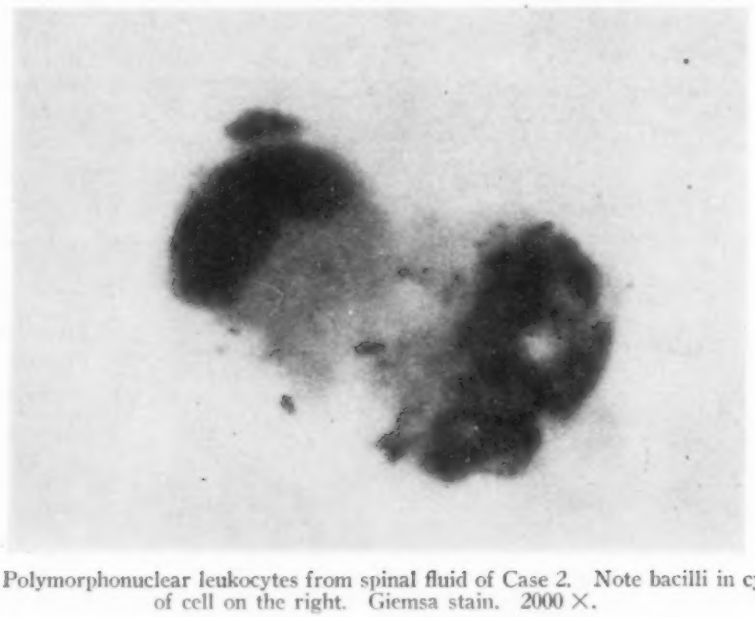

FIG. 2. Polymorphonuclear leukocytes from spinal fluid of Case 2. Note bacilli in cytoplasm of cell on the right. Giemsa stain. 2000 ×.

Case 2. P. S., 43 year old housewife, had had left otitis media of one month's duration accompanied by frontal and occipital headache. Five days before admission, the headache became more severe and nausea and vomiting began. On admission, June 20, 1941, the patient did not appear critically ill and physical examination was not remarkable except for the observation of a foul-smelling discharge from the left ear and a perforation of the left ear drum. The temperature was 99° F., the pulse 70, respirations 20. Spinal fluid, under initial pressure of 150 mm. H_2O, was clear but contained 173 cells per cu. mm., 64 per cent of which were polymorphonuclears.

The following morning the temperature suddenly rose to 104° F., the patient became irrational, and her neck became stiff. The right pupil was smaller than the left and reacted poorly to light. There was almost constant, synchronous, horizontal nystagmus. The spinal fluid was now turbid, containing 40,200 cells per cu. mm., 88 per cent of which were polymorphonuclears. No organisms were seen in the

smear and none grew in cultures incubated aerobically. Sodium sulfapyridine was given intravenously, a blood level of 16.8 mg. per cent being rapidly attained. The temperature remained high, and lumbar puncture on the third day yielded turbid fluid under 310 mm. H_2O pressure, with 25,000 cells per cu. mm. (90 per cent polymorphonuclears). A few cells contained small gram-negative bacilli, 1 to 2 micra in length (figure 3). These organisms grew in anaerobic cultures.

Mastoidectomy * on the third day revealed granulations in the mastoid cells and pus draining from a defect in the tegmen. An extradural abscess consisting of an area of granulation 1 cm. in diameter was found. Bone was removed until healthy dura was exposed. The sinus appeared normal. The cerebellar dura was coated with a fine layer of fibrin. The patient died early the following morning.

Laboratory data. The red blood cell count was 3,480,000 cells per cu. mm., the hemoglobin 71 per cent. The white blood cell count rose from 12,300 to 31,600 (80 per cent polymorphonuclears).

Autopsy. In the temporal lobe, just above the extradural abscess noted at operation, there was a brain abscess, 3 cm. in diameter, extending medially to communicate with the inferior horn of the lateral ventricle. Both lateral ventricles were coated with purulent exudate. There was very little subarachnoid exudate over the base of the brain. Both cerebellar and tentorial pressure cones were present. Two small recent infarcts were found in the lower lobe of the left lung.

Bacteriology. The organism recovered from the spinal fluid of this case exhibited morphological and cultural characteristics similar to those noted for the organism recovered from case 1, and we regard it as another strain of *Bacteroides fundulifórmis.*

Case 3. N. D., 50 year old laborer, had had chronic bilateral otitis media for many years. Two weeks before admission the right ear became painful, and three days before admission a polyp was removed from this ear at another hospital. The day before entry the patient developed severe occipital headache and nausea and within a few hours began to have pain in the neck and back.

On admission, October 22, 1942, he was semicomatose, his neck was stiff, and Kernig's sign was present bilaterally. The right ear drum was obscured by sulfanilamide crystals which had been introduced at the time of excision of the polyp and may have impeded drainage. No discharge was noted in the canal. The left ear drum showed a large perforation from which foul pus drained. The temperature was 102° F., the pulse 118, respirations 24. The remainder of the physical examination was not remarkable. Spinal fluid was turbid, containing 4,290 cells per cu. mm., 94 per cent of which were polymorphonuclears. No organisms were seen in the direct smear of this or of any subsequent samples of spinal fluid.

Right radical mastoidectomy † was performed on the day of admission. Yellow-green, not particularly foul pus was found in the antrum. There was no pus over the dura. Sulfadiazine therapy was given as indicated in chart 2.

The next day the patient was quite rational. Lumbar puncture revealed turbid fluid containing 3,120 cells per cu. mm. Cultures of this fluid incubated anaerobically yielded *Bacteroides.* The patient improved rapidly and on the eighth hospital day seemed well.

Sulfadiazine therapy was discontinued on the sixth day because of the appearance of red blood cells in the urine. Nine days later the temperature suddenly rose to 102.5° F., and there was a return of headache and drowsiness. The drug was readministered, and the temperature returned to normal within four days. The patient was continued on 2.5 grams sulfadiazine daily for three weeks. During this time his temperature remained normal but a right facial paralysis developed.

* Operator, Dr. E. F. Lawlor.
† Operator, Dr. Francis L. Weille.

Revision of the mastoidectomy * was performed and granulations removed in an effort to relieve the facial paralysis. Another episode of fever and stiffness of the neck followed this operation, and sulfadiazine was again administered. The temperature returned to normal after six days. Sulfadiazine was again continued for three weeks. The patient was discharged well on the eighty-fourth day. The facial paralysis had improved considerably.

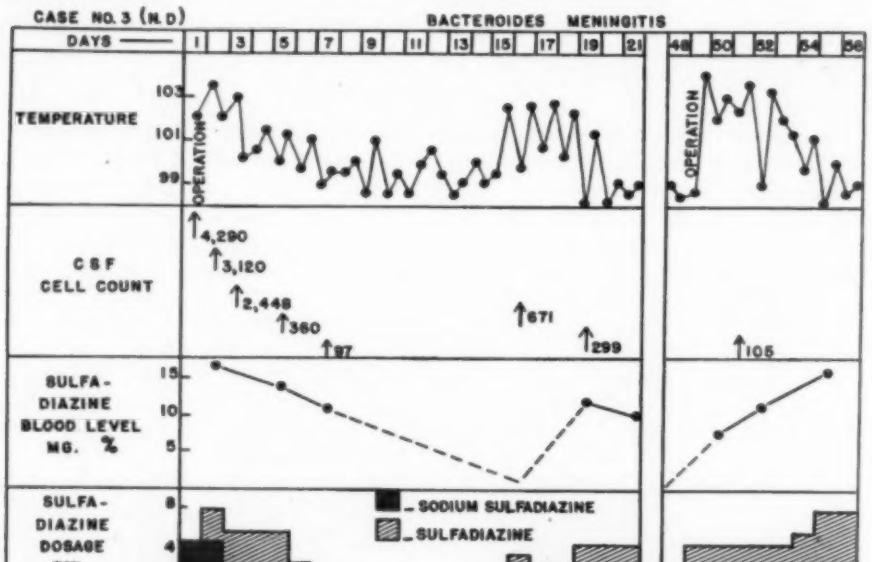

CHART 2.

Laboratory data. The red blood cell count ranged between 4,230,000 and 3,160,000 cells per cu. mm., the hemoglobin between 74 and 57 per cent, and the white blood cell count between 5,000 and 12,000 cells per cu. mm. (70 to 80 per cent polymorphonuclears). The urine was not abnormal.

Data on several samples of spinal fluid are given below.

Date	Pressure mm. H_2O Initial/Final	Cell Count	PMN %	Lymph. %	Sugar mg. %	Protein mg. %
Oct. 22	295/180	4290	94	6	35	444
24	450/300	2448	50	50		78
28	180/120	97	24	76	50	51
Nov. 6	160/120	671	65	35	54	105
13		98	16	84	57	59
Dec. 10	220/130	105	81	19	50	182

Chlorides were determined as 656 mg. per cent on November 6, 685 mg. per cent on November 13. A gold sol curve on November 6 was read 0012231100.

Bacteriology. The organism grew out after 72 hours in a meat tube enriched with ascitic fluid and incubated in an anaerobic jar. There was diffuse turbidity and

* Operator, Dr. Philip Mysel.

a foul odor. Colonies on anaerobic blood agar plates were smooth, gray, non-hemolytic, low convex, with entire edge, attaining a diameter of 0.2 to 0.5 mm. after 48 hours' incubation. On moist ascitic agar plates this strain developed very large mucoid colonies as the result of the formation of large capsules. The organisms were very small bacilli, about 1 micron in length and 0.5 micron in width. They often occurred as diplobacilli enveloped within a heavy capsule. Occasional longer individuals were seen. Chain formation was not observed. They were gram-negative, non-motile and strictly anaerobic.

A few rough-surfaced colonies with fimbriate edge also appeared in the cultures. These were composed of non-capsulated, gram-negative bacilli 5 to 8 micra in length with pointed ends. These long bacilli could be transferred on plates but failed to grow in pure culture in liquid media. They may have been a rough variant of the mucoid organism, or they may have been a separate species of the genus *Fusobacterium.*

These observations are similar to those of Klinger,[7] who cultivated a small encapsulated anaerobic bacillus from a brain abscess. His bacillus has since been named *B. mucosum.*[20] Klinger also noted the presence of long pointed bacilli in his cultures, which he regarded as *B. fusiforme.*

Case 4. M. D., 37 year old waitress, had had a discharge from the left ear for 18 years. She entered the hospital on November 16, 1942, with complaint of left earache of six days' duration, nausea, vomiting, and vertigo of one day's duration. She did not appear seriously ill, and physical examination was essentially negative except for the observation of a serous and bloody discharge and a polyp in the left ear. The temperature was 99° F., the pulse 76, respirations 20.

First stage radical mastoidectomy was performed on November 20, the second stage on November 27, and the patient did well until December 8 when left facial paralysis appeared. On December 14 (day 4 in the chart) the temperature suddenly rose to 105° F., the neck became stiff, the eyes were held constantly to the right, and Kernig's sign was noted bilaterally. Spinal fluid was turbid but sterile (aerobic and anaerobic cultures). The mastoidectomy was revised and labyrinthectomy performed.* The cerebral dura and the lateral sinus were found covered with granulations. The cerebellar dura had been eroded and exuded necrotic material and seromucoid pus. Two fistulae were found in the lateral semicircular canal, which contained pus. Sulfadiazine therapy was given as indicated in chart 3. Lumbar punctures and intravenous saline and glucose infusions were carried out almost daily during the succeeding two weeks. One transfusion was given.

The temperature remained elevated for two weeks but was essentially normal thereafter. The patient showed inability to gaze to the left, bilateral papilledema, absent corneal reflex on the left and complete peripheral paralysis of the left facial nerve and the left sixth nerve. Muscle strength and coördination were impaired in the left arm. There were positive Babinski reflexes and unsustained ankle clonus bilaterally.

On January 4 a left occipital incision was made and a ventricular needle introduced.† At a depth of 4 cm. in the anterolateral region of the cerebellum, an abscess was encountered after the resistance of an apparently thick capsule was overcome. Ten c.c. of fairly fluid, yellowish material with a sour odor were aspirated and an equal amount of thorotrast was placed in the abscess cavity. Three more tappings were performed in the succeeding month. The first tapping yielded an abundant growth of *Bacteroides,* the second only a few colonies, the third and fourth were

* Operator, Dr. Edgar Holmes.
† Operator, Dr. Jost Michelsen.

sterile. Sulfadiazine therapy was continued until February 17, the blood level being maintained at about 10 mg. per cent.

The patient improved gradually and was discharged well on the one hundred twenty-ninth hospital day with residual facial paralysis and left adiadokokinesis.

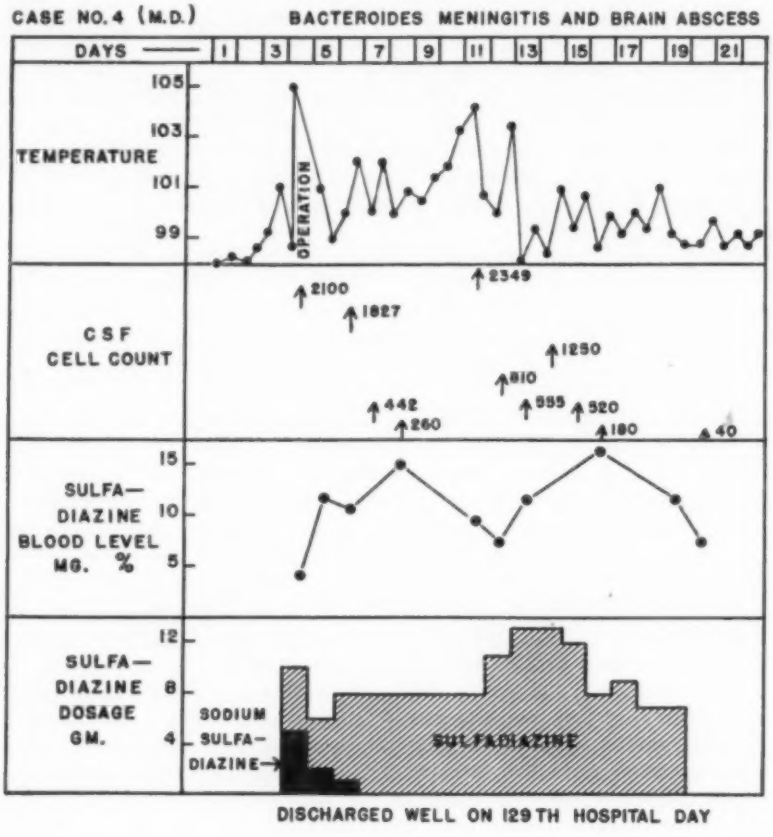

CHART 3.

Laboratory. The red blood cell count ranged between 3,606,000 and 2,666,000 cells per cu. mm., the hemoglobin between 70 and 62 per cent, and the white blood cell count between 16,700 and 8,400 cells per cu. mm. (90 to 86 per cent polymorphonuclears). The urine often contained albumin and white blood cells.

Representative spinal fluid studies are:

Date	Pressure mm. H_2O Initial/Final	Cell Count	PMN %	Lymph. %	Sugar mg. %	Protein mg. %
Dec. 14	700	2100	80	20	81	576
16	525/260	1827	92	8	45	75
18	300/100	260	48	52	62	67
24	300/100	1250	81	19	44	84
26	160/ 70	180	75	25	61	98
30	180/ 50	40	47	53		

Chlorides were determined as 656 mg. per cent on December 14, 683 mg. per cent on December 18.

Bacteriology. Organisms were never demonstrated in the spinal fluid. Pus from the brain abscess yielded gram-positive cocci in chains and gram-negative bacilli in infusion broth. The cocci failed to grow on subcultures and were not seen in subsequent samples of pus from the abscess. The bacilli grew in subcultures, but only under anaerobic conditions. They produced a few bubbles of gas and diffuse turbidity after 48 hours' incubation in meat tubes enriched with ascitic fluid. Chain formation was not observed, nor did the cultures have a foul odor. Colonies on blood agar plates were smooth, gray white, low convex with entire edge, easily emulsifiable and attained a diameter of 1 mm. after 48 hours' incubation. They were non-hemolytic.

These organisms were straight, slender rods 1 to 2 micra in length with occasional longer individuals up to 6 micra in length. Free large bodies and individuals with a bulbous swelling at one end or in the middle were occasionally seen but were not numerous. The bacilli were non-motile, did not produce indol but did form hydrogen sulfide. They were killed by a temperature of 60° C. maintained for 20 minutes. Neither spores nor capsules were observed.

A comparison of this description with that of the bacillus from Case 1 brings out many points of difference. According to Lewis and Rettger's classification of *Bacteroides* from feces, this strain might be regarded as *B. vulgatus*.[22, 23] Nevertheless, its derivation from a brain abscess and its considerable pleomorphism inclines us to place it tentatively in the *B. fundulifórmis* group.

Discussion

On the basis of the cases just presented and those described in the literature, the following conclusions appear warranted.

Bacteroides infection of the central nervous system arises most commonly from chronic otitis media. It occurs in both males and females, more commonly in adults than in children, and its symptomatology corresponds with that seen in other pyogenic infections of the central nervous system. The onset of *Bacteroides* meningitis is acute and signalized by fever, headache and stiffness of the neck. The onset of *Bacteroides* brain abscess is less dramatic and may be marked only by headache and vomiting. The possibility of *Bacteroides* infection should be considered when either syndrome occurs in a patient with chronic otitis. In cases of brain abscess, the spinal fluid may be clear. In cases of meningitis, the fluid is cloudy, the cell count ranging from 2,000 to 45,000 cells per cu. mm., the sugar content being decreased whereas the protein is increased. Diagnosis depends upon cultivation of the organisms, and anaerobic cultures should be made repeatedly in cases in which gram-negative bacilli are seen in smears or in which aerobic cultures are sterile. The course may be acute with death occurring between the fourth and ninth days in fatal cases. Recovery, when it occurs, may be prompt or prolonged, depending upon the severity of the meningitis and the presence or absence of brain abscess.

The *Bacteroides* are pyogenic organisms. The exudate in the meninges and the pus in the brain abscesses are composed of polymorphonuclear cells,

and organisms can usually be demonstrated in direct smears as gram-negative bacilli lying both intra- and extracellularly. They may be mistaken for influenza bacilli unless cultural studies are made. In Case 3, organisms were cultivated from a spinal fluid in which they were present in such small numbers that they could not be found in direct smears. This case might have been regarded as a so-called "sterile meningitis" if anaerobic cultures had not been made repeatedly. *Bacteroides* meningitis is usually most extensive over the base of the brain but may be localized to a small area adjacent to the infected ear. In Case 2 the meningitis arose from the rupture of a brain abscess apparently precipitated by withdrawal of spinal fluid by lumbar puncture. Cranial nerves, particularly the facial, are apt to be involved. *Bacteroides* brain abscess usually occurs in the temporal lobe on the same side as the infected ear, but may be elsewhere as in Case 4 where the abscess was in the ipsilateral lobe of the cerebellum or in Newhart's case where it was in the contralateral lobe of the cerebellum. Sinus thrombosis is a frequent complication, and, when this occurs, invasion of the blood stream with the development of septic infarcts in the lung is common.

On the basis of the cases already in the literature, the prognosis would appear hopeless. The recovery of three of our four patients is, therefore, of particular interest. Three factors which may have aided recovery are more adequate surgical and supportive treatment and chemotherapy.

From table 1 it is seen that mastoidectomy was performed in all but three of the reported cases, in several at an early stage of the disease. Repeated lumbar punctures were not performed, however, nor were brain abscesses drained except in Newhart's case. With the exception of Newhart's case, which received sulfanilamide and transfusions, the other preceding cases were collected from the older literature and were cases treated before the value of intravenous fluids and transfusions was recognized. They cannot, therefore, be regarded as strictly comparable controls in evaluating the third factor, chemotherapy.

Sulfapyridine did not appear of value in Case 1, since this patient recovered only after a very prolonged illness. Intravenous fluids and transfusions were certainly of great importance in this case. Case 2 also received sulfapyridine, but died too quickly to evaluate chemotherapy. In Case 3, however, it seemed apparent that sulfadiazine affected the course favorably as the infection subsided promptly on three different occasions coincidently with the administration of this drug. In Case 4, also treated with sulfadiazine, the meningitis cleared up promptly when this drug was given, but the drainage of the brain abscess was undoubtedly a major factor in the patient's recovery.

The possibility that variations in clinical course are due to varying degrees of virulence of different strains of *Bacteroides* cannot be evaluated until more adequate criteria of species differentiation are available and more cases have been observed. Speculations based on studies of animal pathogenicity may be misleading.

The conclusion may be drawn that the treatment of choice at present would appear to consist of early and adequate surgical procedures to remove foci of infection in the ear and mastoid, repeated lumbar punctures for drainage of meningitis, appropriate measures for drainage of brain abscess, attention to indications for intravenous fluids and transfusions, and sulfadiazine therapy. This conclusion is in harmony with that of Burman et al.,[24] who recently reported a series of 38 cases of otitic meningitis due to the common aerobic pyogenic organisms.

Note.—Since the submission of this paper, we have seen a fifth case of *Bacteroides* meningitis. The infection in this case also arose from chronic otitis media. The patient recovered. The case has been described elsewhere.[26] In all, 20 cases of *Bacteroides* infections, including septicemias, peritonitis and various localized processes have been seen at this hospital within the past four years. A review of these cases is being prepared by one of us.[27]

Summary

Two cases of meningitis and two cases of brain abscess due to anaerobic bacilli (*Bacteroides*) are described. A review is given of previously reported cases, all of which were fatal. Three of the four patients described in the present paper recovered. Treatment is discussed. Anaerobic cultures should be made in cases of meningitis or brain abscess, especially those of otitic origin, when gram-negative bacilli are seen in smears or when no organisms can be cultivated aerobically. Primary isolation of *Bacteroides* is greatly facilitated by addition of 30 per cent ascitic fluid to the media.

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GALL-BLADDER DISEASE IN ELDERLY PATIENTS*

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THE finding of gall-bladder disease in the course of autopsies on patients of advanced age is more than an occasional occurrence. The figures given by different authors vary. According to Kaufmann,[1] gall-stones were found in 10.9 per cent of 10,025 autopsies in Basle, two-thirds of them being women. Mentzner,[2] of the Mayo Clinic, found pathological evidence of gall-bladder disease in 62 per cent of the patients over 21 years of age operated upon there, 21.7 per cent of all autopsied adults having gall-stones. Crump,[3] on the basis of 1,000 autopsies performed in Vienna on patients, 80 per cent of whom were over 40, reported statistics showing that the incidence of gall-stones was 22.5 per cent in the males and 26.5 per cent in the females. Burton,[4] in a series of 100 consecutive autopsies at Glasgow, found 10 per cent had cholelithiasis, 30 per cent had cholecystitis and 5 per cent had cholesterosis.

In the group of patients which we have studied, we have been able to corroborate this general conclusion; namely, that gall-bladder disease, and particularly gall-stones, are frequently found during the course of routine autopsies of elderly patients. Such findings are incidental, are not anticipated at the time of postmortem examination nor preceded by symptoms which would make their presence suspected during life. Our general autopsy observation has, therefore, led us to the impression that gall-bladder abnormalities in this group present features which differ both clinically and pathologically from those seen in the younger age group.

Type of Material Studied. Our study concerns itself principally with patients in the latter decades of life, 89 per cent of the cases studied having been above 50 years of age and 73 per cent above 60 years of age.

We have thus reviewed an unselected group of 300 autopsies performed successively over a period of about three years (1934–1937) on patients of the Neurological Hospital and City Home, who had been on the wards for some time and in many instances for several years. Included in this number were 179 males and 121 females (table 1). Of the entire group of 300 cases, 115 or 38 per cent showed some form of gall-bladder disease, 33 per cent of the males and 46 per cent of the females showing abnormality of the gall-bladder.

To obtain an accurate impression of the relative incidence of gall-bladder disease, it is essential to subdivide the cases by age decades, for it is well known that in early life, very little gall-bladder disease is encountered,

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whereas in later life, particularly beginning with the fourth decade, the incidence of gall-bladder disease increases with the advancing age of the patients. We found the largest percentage of disease in the seventh decade, where 65 per cent of the females showed some form of gall-bladder abnormality. This figure appears to be high, but it parallels the presence of gall-

TABLE I
Gall-Bladder Disease

Number of Autopsies			Number Showing Disease			Per Cent Showing Disease		
Male	Female	Total	Male	Female	Total	% of Total Autopsies Showing Disease	% Total Male	% Total Female
179	121	300	59	56	115	38.7%	33%	46%

stones in this age group which for females is 54 per cent of the total number of patients. Correspondingly, the incidence of gall-bladder disease in males of this decade is 40 per cent. Interesting also is the fact that in the eighth decade, the incidence of such disease is almost equal in both sexes (50 per cent of the males and 47 per cent of the females). The figures for the ninth decade are too small to warrant analysis (table 2).

TABLE II
Gall-Bladder Disease by Decades

Ages	Total Cases	Total Disease	% Disease	Number Male Cases	Number Showing Disease	% Disease	Number Female Cases	Number Showing Disease	% Disease
10–19	3	0	—	2			1	0	—
20–29	4	0	—	4			0	0	—
30–39	7	0	—	4			3	0	—
40–49	19	5	26	9	2	22	10	3	30
50–59	47	13	28	27	6	22	20	7	35
60–69	78	29	37	45	15	33	33	14	43
70–79	104	50	48	69	27	40	35	23	65
80–89	35	17	49	18	9	50	17	8	47
90–99	3	1	33	1	0	—	2	1	50
	300	115		179	59		121	56	

Type of Pathologic Lesion. Upon classifying the various abnormalities encountered (table 3), it was seen that the cases having stones in the gall-bladder comprised the largest group (64 per cent). In this number there were included those cases in which frank concretions of appreciable size were found. This finding was frequently associated with abnormalities of the gall-bladder wall. The number of cases showing cholecystitis grossly but having no stones was relatively small. Those cases described as having enlarged or distended gall-bladders without stones and without marked change in the color of the bile were instances in which the gall-bladder disease was

TABLE III

Types of Gall-Bladder Disease

Gall-stones	74
Sand	8
Distended gall-bladder	14
Hydrops	6
Chronic cholecystitis or thickened gall-bladder	4
Pericholecystitis or adhesions	4
Diverticuli	1
Carcinoma with stones	2
Carcinoma without stones	1
Hemorrhagic area	1
Total	115

apparently of recent origin and probably related to the terminal stage of the patient's disease. These cases of distended gall-bladder with a more aqueous fluid, called hydrops of the gall-bladder, were of somewhat longer duration. The cases described as showing sand include gall-bladders containing inspissated bile of recent formation as well as small granular particles which in some cases were cholesterol precipitates. Not included in this number were two cases in which the gall-bladder had been removed surgically, apparently due to preëxisting disease.

Gall-Stones. There were altogether 78 cases with gall-stones in our series of 300 (table 4). Of these, 36 were in males and 42 in females. The

TABLE IV

Gall-Stones

Incidence by Decades

Ages	Males			Females		
	Total No. of Cases	No. Showing Gall-Stones	% of Total	Total No. of Cases	No. Showing Gall-Stones	% of Total
10–39	10			4		
40–49	9	1	11	10	2	20
50–59	27	4	15	20	5	25
60–69	45	7	15	33	12	36
70–79	69	17	25	35	19	54
80–89	18	7	38	17	4	24
90–99	1	—		2	—	
Total	179	36		121	42	

frequency of occurrence of gall-stones was related to the incidence of general gall-bladder disease. This finding was relatively more common in females. In the sixth and seventh decades, the proportion of females that had stones, to the males of the same category, was about 2 to 1. In the eighth decade, however, the males with cholelithiasis exceeded the females by an appreciable figure (male 38 per cent, female 24 per cent).

Type of Gall-Stones. An accurate description of the stones is not available. They were described grossly as follows:

1. *Single stones* of variable sizes and of hard consistency, frequently described as of cholesterin within a bilirubin shell; occasionally described as being a cast of the gall-bladder; sometimes associated with stone in the common duct.

   Total number of cases—20

2. *Two stones,* similar in type to the one described above.

   Total number of cases—6

3. *Multiple stones,* 3 to 100 small stones usually described as being small and faceted.

   Total number of cases—48

4. *Stone in the common duct only,* similar to any of the above, but found only in the common duct.

   Total number of cases—2

5. No description given.

   Total number of cases—2

Relation of Gall-Bladder Lesions to Gall-Stones. Of interest is the condition of the gall-bladder wall in cases with and without gall-stones. Accordingly, sections of the walls of 60 gall-bladders of autopsied cases of the Welfare Hospital, which were available, were examined (table 5). These comprised single sections and at most several sections of each gall-bladder of cases with and without stones.

TABLE V

Relationship of Cholecystitis and Cholelithiasis

Analysis of 60 Cases

	Gall-Stones Present		Gall-Stones Absent	
	No.	%	No.	%
Cholecystitis—active	6	18	0	0
Cholecystitis—healed	19	56	5	19
Cholecystitis—absent	9	26	21	81
Total	34	100	26	100

It must be pointed out here that the examination of gall-bladders in autopsy material is highly unsatisfactory as postmortem changes set in rapidly after death, particularly in the mucosa of the organ. Furthermore, the criteria for inflammatory change, especially as to the degree of acuteness or chronicity, are not entirely satisfactory. Hence the terms active and healed are used, the former when the inflammatory process is essentially cellular and the latter when the process is essentially fibrotic. In these latter cases, the combination of connective tissue replacement, thickening and deformity of the walls of the blood vessels, with or without cellular increase, was taken as evidence of previous inflammation.

Of the 60 cases studied (table 5), 34 cases had gall-stones; the remaining 26 were free from stones. From the table, it can be seen that 74 per cent of the cases having gall-stones showed some form of gall-bladder disease, whereas only 19 per cent of those not having gall-stones had similar lesions. The former figure is probably high since in routine autopsies, sections are more apt to be taken of organs where disease is suspected. Furthermore, 18 per cent of those with stones showed evidence of active inflammation, whereas none of those without stones showed a similar degree of inflammation.

Because the number of cases is small, the figures are mentioned with reservation. However, the association of cholecystitis and cholelithiasis is indicated, and is in agreement with usually accepted opinion.

Symptomatology of Gall-Stones. Having encountered gall-stones so frequently in the course of routine autopsies, we were interested in comparing these autopsy findings with the clinical histories of the patients. Divergent views exist in the literature concerning the symptomatology of cholelithiasis. Moynihan [5] states all gall-stones, except pure cholesterin stones, invariably cause symptoms. Mayo [6] has written of the "myth" of symptomless gall-stones. On the other hand, Rowlands [7] gives the frequency with which such calculi produce symptoms as 10 per cent. Burton [4] stated that in his series of 100 autopsies, out of 10 which showed gall-stones at autopsies, six had had no symptoms.

In our series of 78 cases with cholelithiasis, the clinical facts were as follows:

1. *Cases essentially without symptoms of calculus:* These were cases which presented no symptoms diagnostic of gall-bladder disease. In the majority of cases no abdominal complaints were recorded in the clinical histories. In some cases abdominal symptoms when present were ascribed to the associated disease, such as cardiac decompensation, carcinoma of the stomach, etc.

   Total number of cases—52 or 67 per cent

2. *Cases with vague abdominal symptoms:* These were indefinite, not clinically diagnostic and consisted usually of mild pain in upper abdomen, constipation and occasional vomiting. One case not included in this series was based on the accidental finding of a gall-stone shadow during the course of a gastrointestinal roentgen series. Included in this group were two cases which were diagnosed as acute appendicitis but which on laparotomy were found to have acute cholecystitis.

   Total number of cases—12 or 15 per cent

3. *Cases with definite symptoms:* In these the clinical symptoms were sufficiently definite to warrant a diagnosis of gall-bladder disease, such a diagnosis having been made during the life of the patient.

   Total number of cases—12 or 15 per cent

4. *Operated cases:* These had been operated upon at an outside hospital and were without symptoms while at the Neurological Hospital.

Total number of cases—2 or 3 per cent

In these cases in which a definite diagnosis of gall-bladder disease was made during the life of the patient, seven had typical attacks of gall-bladder colic with or without jaundice. Three had atypical attacks or right upper quadrant pain lasting for many hours. Two had continuous pain accompanied by fever and lasting for several days. Jaundice having its origin in gall-bladder disease was found altogether in eight cases. In this series were not included those instances in which the jaundice was associated with liver lesions other than that due to gall-bladder disease.

It can be seen, therefore, that only 12 cases out of 78 or 15 per cent of the total number of cases having gall-stones, showed evidence sufficiently characteristic to warrant a definite diagnosis of cholelithiasis. If the two cases operated upon are included, this figure will be 18 per cent, and if the two cases of suspected acute appendicitis which were really acute cholecystitis with cholelithiasis are included, the number will reach 21 per cent. The majority of our cases gave no symptoms sufficient to warrant a definite diagnosis of cholelithiasis. Inasmuch as the figures represent mostly individuals in the sixth, seventh and eighth decades of life, the incidence of cholelithiasis presumably did not shorten the span of life of these patients.

This analysis is not meant to imply that all gall-bladder disease is without importance in advanced age, since acute disease of the gall-bladder in old people is frequently a serious surgical problem. This study is rather meant to convey that not all gall-bladder disease in advanced age, and particularly that not all gall-stones, offer a serious prognosis.

However, in the "asymptomatic" type of gall-bladder disease that we have reviewed, neither the number nor size of gall-stones nor even the condition of the gall-bladder necessarily had any bearing on the presence of diagnostic symptoms. For in our cases there were instances of both single and multiple stones, faceted and round, without symptoms. In some cases the gall-bladder was distorted, thickened, sometimes appearing as a purse drawn tight over one or multiple stones, without symptoms and unsuspected during life. The knowledge that such marked disease may exist without apparent clinical symptoms appears to be important from the point of view that the presence of gall-stones in an elderly patient need not explain all or any of his symptoms.

Association of Gall-Bladder Disease with Liver Disease. In cases in which sections of liver were available, they were examined to determine if associated disease had occurred in the liver. The recognition of such lesions in old patients who may have had a variety of other diseases was obviously difficult. No specific lesions were found in all cases, nor were all cases of gall-stones accompanied by distinct changes in the liver parenchyma. Numerically, however, the cases with gall-bladder disease showed a greater

percentage of liver lesions than those cases without involvement. The changes encountered were periportal accumulation of round cells, periportal fibrosis and occasional foci of lymphocytes in the liver tissue. Rarely also, there was seen cholangitis of the smaller ducts, and duct hyperplasia.

Conclusion

1. Gall-bladder disease is frequently encountered in autopsies of elderly patients of both sexes. In the fifth to the eighth decade, the percentage is relatively larger in the females, but in the eighth decade, the incidence of such disease is somewhat higher in the males.

2. Gall-stones are found with a corresponding frequency, so that in the seventh decade, 25 per cent of the males and 54 per cent of the females show their presence, and in the eighth decade 38 per cent of the males and 24 per cent of the females have stones.

3. Evidences of previous cholecystitis are found in most cases of cholelithiasis.

4. Gall-bladder disease and particularly gall-stones are frequently encountered in the autopsies of elderly patients who, during life, had no clinical history diagnostic of cholecystitis or cholelithiasis.

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PANCREATIC LITHIASIS *

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THE purpose of this paper is to report two cases of pancreatic lithiasis, each of which presents different aspects of the same clinical syndrome. The first case is an alcoholic who showed early disturbance in the sugar metabolism, yet the pancreatic disease had not presented a serious threat to life. The second case succumbed to progressive disease of the pancreas, yet she was not an alcoholic and developed no serious disturbance in sugar metabolism until a few days before death.

CASE REPORTS

Case 1. (Mrs. A. B.) The patient, a 54 year old white female, had been seen at frequent intervals since 1937 with the complaint of upper abdominal pain and vomiting which usually followed overindulgence in alcohol.

Past History: She had always had good health except for a ruptured appendix in 1926 and a hemorrhoidectomy in 1930. She had had three normal pregnancies. She used alcohol, bromides and the barbiturates freely for several years prior to 1937, but had no illness between 1930 and 1937.

Physical Examination: She was seen for the first time in December 1937 when she had been vomiting for several days, was markedly acidotic and dehydrated, and complained of some upper abdominal pain. She was hospitalized, given fluids by vein, and within a week was much improved. At that time her weight was 133 pounds; blood pressure 110 mm. Hg systolic and 70 mm. diastolic; pulse 110. The blood Wassermann reaction was negative. The blood sugar was 110 mg. per cent. The non-protein nitrogen was 30.0 mg. The urine was negative except for a faint trace of albumin. The blood count was normal. Otherwise the physical examination was not remarkable.

Course: Except for indigestion and some nausea she was well until October 1938 when she began taking alcohol again and vomiting recurred. She had severe right upper abdominal pain, radiating to the back, and on several occasions vomited coffee-ground material which gave a positive guaiac test for blood. During these attacks the stools frequently contained large amounts of fat. Her weight at this time was 143 pounds. The hemoglobin was 62 per cent, and the red cell count was 3,000,000. She had another admission to the hospital with the same complaints and symptoms in December 1938.

During the first three months of 1939, she had almost daily pain and marked tenderness in the right upper abdomen. This was accompanied by a daily temperature rise to 101° F. or more. She was frequently nauseated and had occasional hematemeses. The sedimentation rate was 2.11 mm. by the Rourke method, and there was a moderate leukocytosis. The urine continued to be negative except for a faint trace of albumin. Serum amylase values on three occasions were 40, 68 and 70 units (normal range by Somogyi's method [1]). Lipase was absent from the serum on three different occasions.

In April 1939 an intravenous urogram was done, and showed normal function and filling of the urinary tract. The gastrointestinal series was essentially negative. An oral dye series showed a non-functioning gall-bladder. The intravenous dye

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gave no better results. However, the plates of the abdomen did reveal a group of irregularly calcified shadows lying just to the right of the first lumbar vertebra (figure 1). Oblique exposure showed these radio-opaque areas to be too far posterior to be considered gall-stones. A diagnosis of pancreatic lithiasis was made at this time.

In November 1939, the patient submitted to a cholecystectomy. The gall-bladder was not enlarged. It contained about 10 c.c. of thick, dark green bile, but no calculi were found. Microscopically the wall of the gall-bladder showed slight edema and round cell infiltration. At the time of operation, the pancreas was palpated. The head was considerably enlarged and hard and there was a peculiar crepitus on pressure. No attempt was made to open the pancreas nor remove the calculi.

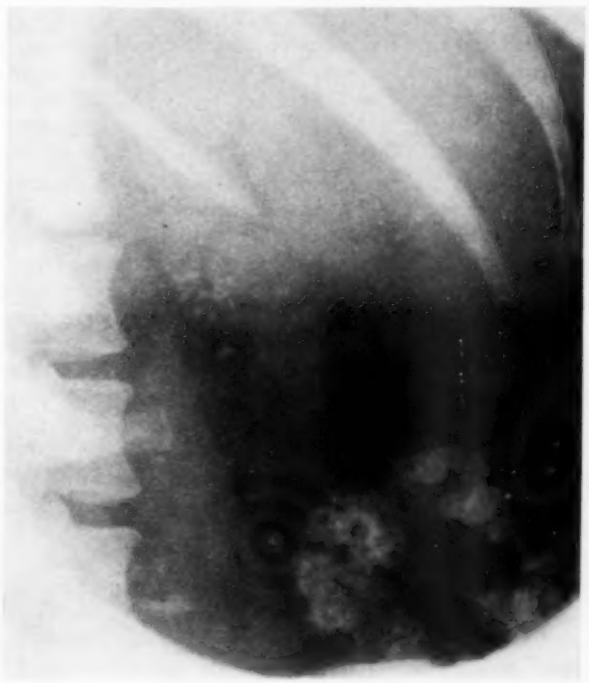

FIG. 1. Calculi in the head of the pancreas.

The patient made a rapid recovery and on discharge from the hospital was started on a fat-free diet along with pancreatic substance. Despite this therapy, the patient continued to have frequent bouts of mild epigastric pain which were initiated by a severe diarrhea. She described her stools as appearing "greasy." She followed her diet fairly well and gained weight, reaching 155 pounds in August 1940.

In November 1940, she complained of excessive thirst, frequency of urination and severe cramps in her legs at night. A fasting urine specimen showed 3 + sugar; the blood sugar was 273 mg. per cent. In December 1940 a sugar tolerance test showed the following results:

Fasting sugar	141 mg.
100 gm. glucose per os	———
½ hour later	161 mg.
1 hour later	200 mg.
2 hours later	243 mg.
3 hours later	220 mg.

All the urine specimens showed a 4 + sugar reaction. She was put on a diabetic diet at this time. However, she would take nothing but alcohol for days and would desist only when vomiting started. In view of the fact that control of her diabetes by dietary methods was manifestly impossible, she was instructed to take 10 units of protamine insulin daily. Under this régime she was free from symptoms if she took no alcohol. Gradually from 1940 to 1942 she tapered off the alcohol intake and became more careful of her diet. She is now living a fairly comfortable existence. Her weight in June 1942 was 155 pounds.

Case 2. (Mrs. C. S.) This patient was a 34 year old colored female admitted to New Rochelle hospital in October 1936. Her chief complaint was severe pain in the epigastrium which radiated to the back. The pain was unrelated to food and was accompanied by fever, chills, malaise and prostration. She had had several attacks of this kind for three years prior to admission.

Past History: She had had the usual childhood diseases in addition to frequent sore throats and occasional joint pains, especially in the knees. At no time were these pains severe enough to cause prolonged bed rest. In 1932 she had had an attack of iritis of the left eye following a direct blow to the eye. She had had three normal deliveries, followed by three still-births.

Physical Examination: She was a well-nourished, colored female who did not seem acutely ill. Her weight was 140 pounds; height 62 inches. The blood pressure was 126 mm. Hg systolic and 70 mm. diastolic; pulse 100; temperature 101° F. The left pupil was irregular and reacted poorly to light and accommodation; the right pupil was normal in appearance and reaction. The tonsils were moderate in size, but showed no evidence of infection. The heart and lungs were essentially negative. There was tenderness and much spasm over the entire upper abdomen, but no masses could be palpated.

Laboratory Findings: The blood Wassermann reaction was negative. The tuberculin test showed a moderate reaction. The leukocyte count was 4,000 with 82 per cent polymorphonuclears and 10 per cent young forms. The hemoglobin was 70 per cent, and the red cell count 4,000,000. A gastrointestinal roentgenographic series showed a normal gastrointestinal tract. An oral dye series showed a normally functioning gall-bladder.

Course: From 1937 to 1940 the patient was seen at another hospital,* where she had frequent admissions for the same complaint, upper abdominal pain. In March 1938, a sugar tolerance test showed a normal curve. In October 1938, an exploratory laparotomy revealed an enlarged liver; the gall-bladder was distended but contained no stones. In palpating the spleen, a firm mass was felt in close proximity to the pedicle. This mass measured 3″ in length by 2″ in width and seemed to be fused with the distal third of the pancreas. It was found impossible to remove this mass because of its proximity to the splenic vessels, but a biopsy specimen was taken. The head and body of the pancreas were firm. A large, firm lymph node was removed for biopsy from the gastrocolic ligament. The patient made an uneventful recovery from the operation.

Microscopic examination of the pancreatic biopsy specimen showed much dense fibrous tissue containing islands of glandular acini and ducts. The ducts were often distended with clear pink-staining material and showed atrophic epithelium. The islands of Langerhans appeared normal. The lymph node was composed entirely of tubercles with large giant cells. A diagnosis of fibrosis of the pancreas and tuberculosis of the retroperitoneal lymph nodes was made.

At discharge the patient was put on a low fat diet and was given pancreatic substance. On readmission in February 1939, her sugar tolerance test showed an

* Permission was granted by Grasslands Hospital, Valhalla, New York, for the use of these data.

early diabetic type of curve. A gastrointestinal series failed to show pancreatic stones or any abnormality of the gastrointestinal tract.

In December 1940, the patient was admitted to New Rochelle hospital with the complaint of failing vision of the left eye. The eye became progressively more painful and was finally enucleated in January 1941. The diagnosis was a non-specific irido-cyclitis with detachment of the retina. During her stay in the hospital she had no abdominal pain but ran a febrile course for several weeks.

FIG. 2. Calculi in the tail of the pancreas.

In March 1941, she was again admitted with the complaint of tightness in the chest, weakness, and gradual loss of weight. She still had a daily fever which often reached 102° F. Her white blood count was 3,100 with 50 per cent polymorphonuclears and 12 per cent young forms. The hemoglobin was 74 per cent with the red cell count 4,200,000. The urinalysis was negative. The sedimentation rate was 1.81 by the Rourke method. The blood urea was 11.7 mg. The blood sugar was 101 mg. Blood cultures were persistently negative. The electrocardiogram was essentially normal. Agglutination tests for typhoid and undulant fevers were negative. The stool examinations were essentially negative except for the finding of large amounts of fat on several occasions. Blood amylase determinations by the Somogyi method never gave values above 100 units (normal range). There were never more than traces of lipase present in the serum. Roentgenographic examina-

tion of the abdomen showed multiple shadows of increased density lying in the cortical region of the left kidney (figure 2). These were interpreted as being pancreatic stones in the tail of the pancreas.

On July 1, 1941, the patient was again admitted because of excruciating abdominal pain. Her temperature was 103° F., and she was semicomatose. The blood sugar was 360 mg., and the urine showed a 4+ reaction for sugar. The carbon dioxide combining power of the blood was 18.0 vol. per cent. Her condition became increasingly worse and on the day following admission she died.

Autopsy Findings: The body was that of an emaciated, 38 year old colored female. The left eye had been removed. There was a midline scar in the upper part of the abdomen. The great omentum was adherent to the scar to the right of the mid-

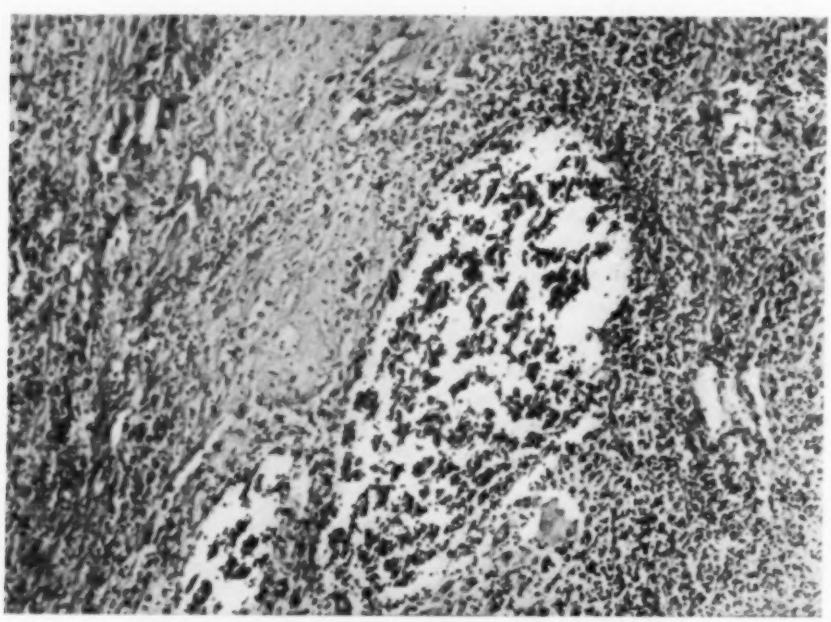

FIG. 3. Section of the pancreas (× 120) showing the marked cellular infiltration with absence of normal glandular elements. Foreign body giant cells are also present.

line. The peritoneal surfaces were smooth and glistening; the peritoneal cavity contained a small amount of serosanguinous fluid. The liver was pale brown in color and not enlarged. The gall-bladder was involved in dense adhesions about the liver; it was distended with about 20 c.c. of thick gelatinous bile; the duct systems were patent. Behind the gastro-hepatic ligament there were enlarged lymph glands which formed a fused mass 8.0 cm. by 2.0 cm. These were pale brown to gray in appearance and on section were adherent to the surface of the pancreas. The pancreas was small and formed a cylindrical mass measuring 10.0 cm. long and 1.5 to 2.0 cm. wide. It was nodular and crepitated on pressure. On section no normal pancreatic tissue was seen; the cut surface had a white, soapy appearance. There were multiple cystic areas scattered throughout the substance of the gland; in many cases these cysts and dilated ducts were filled with a thick, creamy, calcareous material. These deposits measured from 1 mm. to 1 cm. in diameter. The spleen weighed 180 grams and was very soft; on section the pulp was congested. The liver weighed 1,250 grams; on cut section the surface was normal in appearance; the lobular markings were not

prominent. The gastrointestinal tract showed no gross changes. The adrenals appeared normal. The kidneys showed no gross abnormalities. The heart was essentially normal in size and shape. The precordial surfaces were smooth and glistening. The chambers and valves appeared grossly normal. The coronary vessels appeared normal. There was no fluid in the pleural cavities, and no adhesions between lungs and pleura. The lungs were crepitant and the cut surfaces were uniformly pink in appearance and rather moist. There was no consolidation.

Microscopic Examination: The pancreas showed extensive fibrosis and round cell infiltration. In small areas, foreign body giant cells were visible (figure 3). Many dilated ducts were present and were often filled with calcareous material (figure 4). The islands of Langerhans were usually in a better state of preservation

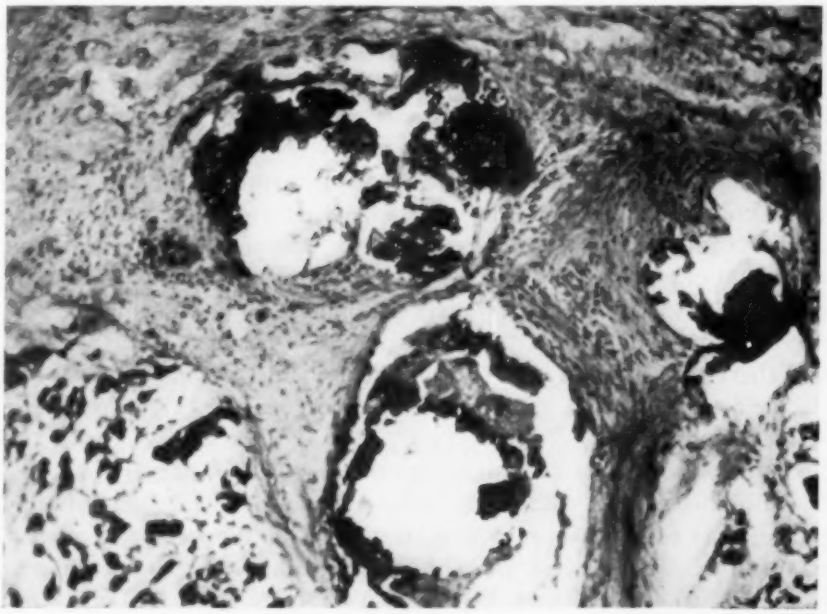

FIG. 4. Section of the pancreas (× 120) showing calcareous material in the alveoli and ducts. There is also an increase in the fibrous tissue of the stroma.

than the acinar tissue, although they also showed hyalinization and necrosis in many areas.

The liver showed a moderate amount of periportal fibrosis and small round cell infiltration. Sections of the rest of the organs showed no noteworthy histopathologic changes.

Gross Anatomic and Microscopic Diagnosis: Chronic pancreatitis with multiple cysts and calculi.

COMMENT

The number of cases of pancreatic disease with lithiasis reported in the literature has more than doubled since 1925, with 102 cases reported prior to that date and 118 subsequently. Whether this represents a true increase in the incidence of the disease or merely a better understanding of its symptomatology with resultant more frequent diagnosis is not apparent at this

time. However, since the disease occurs most commonly in the fourth decade of life, it is probably appearing more frequently as the span of life lengthens.

Pratt [2] maintains that there is no clear-cut symptom-complex for pancreatic lithiasis. However, certain resemblances do exist between cases even so diverse as the two presented in this paper, and it seems worth while to emphasize the prominent symptoms so that the diagnosis may be suspected more often.

(1) *Epigastric pain* (present in both these cases) is the most common and constant clinical symptom of this disease. The pain may be severe in nature and intermittent, or it may be mild and practically constant. It occasionally radiates to the back or to either shoulder. Stones in the tail of the pancreas (as in the case of Mrs. C. S.) may cause left upper quadrant pain with lateral and downward radiation. Nausea, vomiting, fever and chills often accompany the episodes of pain.

(2) *Diarrhea and steatorrhea* are frequent symptoms and usually accompany the colicky pain and vomiting. In the case of Mrs. C. S., the fatty diarrhea became such a prominent symptom that a diagnosis of sprue was considered at one time.

(3) The association of *alcoholism* and pancreatic lithiasis in the reported cases seems far too frequent to be coincidence. In 45 per cent of the cases studied there was a history of chronic alcoholism. As in the case of Mrs. A. B., the attacks of pain, diarrhea and steatorrhea are often precipitated by excessive drinking.

(4) *Disturbances in the carbohydrate metabolism* are frequently associated with this disease. Lazarus [3] found some in 45 per cent of the cases which he reviewed. This may manifest itself by hyperglycemia with glycosuria (as in Mrs. A. B.), or merely by an abnormal sugar curve in the glucose tolerance test (as with Mrs. C. S.)

(5) However, the extent of disturbance of the carbohydrate metabolism bears no apparent relation to the extent of the pancreatic disease nor to the prognosis. In spite of pancreatic therapy and dietary control, Mrs. C. S. lost weight progressively, became cachectic and died; yet she had no serious disturbance of sugar metabolism until a few days before death. At autopsy, the islands of Langerhans were found in a good state of preservation, whereas the acinar tissue was almost completely destroyed. This is similar to the case reported by Barron.[4] On the other hand, Mrs. A. B. showed an early disturbance of the sugar metabolism which progressed to a marked diabetes; yet her pancreatic disease did not present a serious threat to life. She continued to improve in health (as shown by increase in weight and diminution of symptoms) following the cholecystectomy and the institution of pancreatic therapy.

(6) *Liver disease* is occasionally associated with pancreatic stones. Witherspoon [5] described a case with associated portal cirrhosis. The removal of a non-functioning gall-bladder produced considerable improvement in the

symptoms of Mrs. A. B. Mrs. C. S. had normal gall-bladder function, yet portal cirrhosis and fatty infiltration of the periportal areas were found at autopsy.

(7) The time required for *stone formation* is variable since the stones are considered to be the result of a chronic pancreatitis. Snell and Comfort [6] reported one case in which calcification of the pancreas occurred in five years and another in which it required 11 years. Mrs. C. S. had negative abdominal roentgenograms in 1936 and again in 1939; stones were visible in the tail of the pancreas in 1940. However, the patient's symptoms were present from 1936 onward. Mrs. A. B. has had massive calcification in the head of the pancreas since 1939, yet she continues to enjoy a fairly comfortable existence.

(8) *An increase in the serum amylase and lipase* has been reported during the acute phases of pancreatitis.[7, 8] In the two cases presented herewith, there was no significant deviation from normal in either the serum amylase or serum lipase.

Summary and Conclusions

Two cases of pancreatic lithiasis are reported. They illustrate the outstanding features of this disease, namely, upper abdominal crises of pain, radio-opaque calculi in the pancreas, diarrhea, steatorrhea, and disturbances of the internal and external secretions of the pancreas.

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THE NUTRITIONAL RÔLE OF CHOLESTEROL IN HUMAN CORONARY ARTERIOSCLEROSIS *

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Arteriosclerosis, exclusive of the infectious diseases of the arterial system, may be divided pathologically into three types: (1) Atherosclerosis, associated with diseases of the aorta and coronary arteries; (2) arteriolar (or diffuse), sclerosis, associated with arterial hypertension; and (3) Mönckeberg's sclerosis, not clinically significant unless there is superimposed atherosclerosis.

Etiology. Hueper, in a review of the etiology of arteriosclerosis, has concluded that the fundamental causal mechanism is an impairment of nutrition and oxygenation of the artery, resulting in damage to the endothelium, increased permeability of the intima, and infiltration of the plasma into the subintimal tissue with later proliferation of endothelial cells and degeneration of the muscular and elastic elements of the media.[1]

In regard to the etiology of atherosclerosis he states that if the plasma contains temporarily or persistently large amounts of cholesterol or physicochemically related substances forming emulsions with the plasma, there occurs a retention of this material in the proliferating endothelial cells with the ultimate formation of atheromata. This, in general, reflects the current opinion as to the pathologic etiology of coronary arteriosclerosis.

Pathology and Pathogenesis. The histology of atherosclerosis is characterized by lesions with a high cholesterol content localized in the subendothelial stratum of the intima of the artery. There is an early collection of phagocytic cells at this site. These cells contain the cholesterol crystals in both fluid and solid forms. The progression of the lesion involves a proliferation of connective tissue stimulated by the excess cholesterol in the phagocytic cells. There is later invasion of these cells to the deeper strata of the intima. Necrosis occurs here because plasma diffusion is insufficient to nourish the intima. Vascularization results with ultimate repair by connective tissue and finally deposition of calcium.

The formation of these lesions has been related by a number of observers to a disturbance in cholesterol metabolism.[2, 3, 4, 5] The importance of the relationship of other blood lipids to cholesterol as a factor in atherosclerosis has also been emphasized.[6] Atherosclerotic lesions have been produced in the experimental animal, and the methods in these instances are similar. The herbivorous animal is given an excess of cholesterol in the diet, and it has been possible to observe the esterification of cholesterol in the liver and phagocytosis of the excess esters by the reticuloendothelial cells which escape into

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From the Department of Medicine, Henry Ford Hospital.

the circulation and invade the arterial intima.[5] If a carnivorous animal is given an excess of cholesterol in the diet such a process does not occur. Animals vary in their ability to absorb and metabolize cholesterol, and normally the excretion is maintained at an optimum rate for cholesterol balance. But under the circumstances of production of atherosclerosis in the herbivorous animals there is a hypercholesterolemia.

The Nature of Cholesterol. Cholesterol is a hydro-aromatic secondary alcohol which can unite with fatty acids to form esters; it is found in every animal cell. The dietary sources are of animal origin; the plant sterols are not absorbed apparently because of a difference in molecular arrangement. One of the greatest sources for man is found in milk and cream; milk contains about 250 mg. of cholesterol per quart. The human individual can probably manufacture cholesterol but the requirements are met by ingestion. A small fraction is eliminated as cholesterol per se. The greater part is conjugated and excreted in the feces, a smaller part in the urine and some is destroyed in the organism.

The metabolism of cholesterol is presumably regulated by the activity of the reticuloendothelial system rather than by any one organ. Excess cholesterol is difficult to metabolize and remains in the tissues for long periods stimulating connective tissue formation. Certain of the endocrine glands exert a controlling effect on cholesterolemia. The function of the thyroid has an inverse relation to the level of plasma cholesterol. Hyperthyroidism is supposedly associated with no, or mild atherosclerosis and hypothyroidism with moderate atherosclerosis. Bruger and Rosenkrantz have found that hypometabolism in persons over 55 years of age is associated with a significantly greater incidence of arteriosclerosis.[7]

The function of the pancreas is related to the level of plasma cholesterol. There is unanimity of opinion regarding the frequency of hypercholesterolemia in diabetes mellitus and a certain parallelism exists between the level of blood glucose and cholesterol and the severity of the disease. Diabetes is associated with atherosclerosis and several authorities have found that diabetic persons have a significantly greater incidence of angina pectoris and coronary occlusion.[8, 9]

In addition, hypercholesterolemia occurs in association with a number of different conditions including hepatic, splenic and renal diseases. It is present in normal pregnancy. Presumably, because of a more adequate cholesterol metabolism, women are less susceptible to coronary artery sclerosis than men.[5] The only instance in which a hypercholesterolemia has been demonstrated conclusively to be related to human atherosclerosis is in the hereditary endocrine disturbance, xanthomatosis. Muller, in a review of this disorder, has demonstrated a causal relation to coronary arteriosclerosis. He emphasizes the hereditary nature of xanthomatosis which can occur at any age in consecutive generations.[10]

Clinical Study. It has been assumed that nutritional factors, as influenced by the type of diet, have an important rôle in the production of

atherosclerosis in man. From the results of experiments on animals wherein there is a sustained hypercholesterolemia there has been an attempted correlation of observed pathological processes with those in man. The purpose of this study was to determine the effect of the nutritional factor in persons without manifest endocrine disturbances on the incidence of coronary arteriosclerosis as diagnosed by clinical methods. A study of individuals without manifest endocrine disturbances in respect to the determining effect of a sustained hypercholesterolemia on the occurrence of atherosclerosis would be impractical, if not impossible.

The records of over 1,000 patients with duodenal ulcer were reviewed and 100 patients from this group were consecutively selected by simple criteria for comparison with a similar average control. All studied patients were in the age period of 45 to 65, that is, in the period of life when coronary artery disease is most common; 95 per cent of these were men. All of them had been under treatment for an ulcer for not less than five years. The majority had been treated intermittently and periodically for 10 to 15 years, some for as long as 35 years. The average length of treatment in the entire group was 12.5 years. Treatment, in the main, consisted of the use of milk and cream and antacids, no patient being selected for study who had not relied on the use of milk and cream for the relief of discomfort. In such a group it was considered that a history of prolonged intermittent therapeutic use of milk implied an abnormal increase in cholesterol in the diet and met the requirement of a nutritional factor.

Clinical evidence of coronary arteriosclerosis was considered to be coronary artery occlusion with myocardial infarction, angina pectoris and certain conduction disturbances of the heart associated with arteriosclerosis. Symptoms, such as dyspnea, palpitation, and indefinite chest pain, were not considered as evidence of impaired myocardial function, but it is conceivable that a few additional cases in this category might have been the result of coronary artery disease. Physical signs on examination of the heart itself were not included because of the variable factor of different personal interpretation in a large control group. However, such omissions are immaterial for comparison.

Results

Of 100 patients, three had a coronary artery occlusion with myocardial infarction. In this group there were two men and one woman; their average age was 60; and the duration of ulcer treatment was 10, 15 and 20 years respectively. There was one case of doubtful myocardial infarction, that of a sudden postoperative death from either coronary occlusion or pulmonary embolism in which no postmortem examination could be made to establish the diagnosis.

Three patients had angina pectoris and another three had either or both clinical and electrocardiographic evidence of arteriosclerotic heart disease. These were all men, their average age was 55; and the average duration of

ulcer treatment was 15.0 years. The remainder of the total group of 100 cases included one case of possible arteriosclerotic heart disease based on clinical evidence. All of these had adequate cardiovascular histories and examinations recorded. There was a total of 9 per cent of cases in the studied group with definite evidence of coronary artery sclerosis. The results are summarized in table 1.

TABLE I

Patient	Clinical Diagnosis	Electrocardiographic Diagnosis
1	Coronary occlusion, myocardial infarct	Myocardial infarction, anterior type
2	Coronary occlusion, myocardial infarct	Myocardial infarction, anterior type
3	Coronary occlusion, myocardial infarct	Myocardial infarction, posterior type
4	Pulmonary infarct or myocardial infarct	Negative
5	Angina pectoris	Negative
6	Angina pectoris	Inverted T in Leads I and IVF
7	Angina pectoris	Small R in Lead IVF
8	Arteriosclerotic heart disease	Auricular fibrillation
9	Arteriosclerotic heart disease	Complete bundle branch block
10	Arteriosclerotic heart disease	Not done
11– 24	Other	Normal
25–100	Other	Not done

Five hundred patients were used as a control. These were also consecutively selected from hospital admissions, were in the same age period, 45 to 65, with the same sex ratio, 475 males and 25 females. None of these individuals had received peptic ulcer treatment or had any manifest endocrine disturbance. An identical 3 per cent had a coronary artery occlusion, 2.5 per cent had angina pectoris, and 5 per cent had arteriosclerotic heart disease. The latter diagnosis was based on both clinical and electrocardiographic evidence in each case and rigid criteria were used. Clinical evidence was cardiac failure with an arteriosclerotic basis; electrocardiograms exhibited either the conduction disorders associated with arteriosclerosis, evidence of a previous coronary occlusion, or abnormal QRS complexes or inverted T-waves in Leads I, I and II, or I and IV. Ten patients with the single abnormality of a Q-wave in Lead III larger than 25 per cent of the greatest excursion of QRS were not included. All patients with arterial hyperten-

TABLE II

Patient	Clinical Diagnosis	Electrocardiographic Diagnosis
1– 10	Coronary occlusion, myocardial infarct	Myocardial infarction, anterior type
11– 15	Coronary occlusion, myocardial infarct	Myocardial infarction, posterior type
16	Coronary occlusion, myocardial infarct	Myocardial infarction, combined anterior and posterior
17– 30	Angina pectoris	Variable
31– 55	Arteriosclerotic heart disease	Includes: auricular fibrillation, partial heart block, complete heart block, incomplete bundle branch block, complete bundle branch block, or abnormal QRS and/or T-waves
56– 65	No or possible heart disease	Large Q-wave in Lead III
66– 79	Hypertensive heart disease	Abnormal QRS and/or T-waves
80–135	No or other heart disease	Variable
136–500	Other	Not done

sion and electrocardiographic abnormalities were excluded to avoid possible confusion with arteriosclerotic heart disease. Of the patients in the control group, 10.5 per cent had definite evidence of coronary artery sclerosis. These results are summarized in table 2.

Comment

It is evident that the incidence of coronary arteriosclerosis in the studied group is no greater than in a similar average control group. Research in coronary artery disease is comparatively recent and the statistical comparison of these results with other sources of information may be of doubtful value. Available information includes a report by Levy and his associates who quote the incidence of coronary artery occlusion with myocardial infarction at 10 per cent for the age period of 45 to 64.[11] In another report Willius et al. studied over 5,000 consecutive autopsies and graded the extent of coronary arteriosclerosis from 0 to 4. In the fifth decade, which would denote an average age of 55, the combined total in over 1,000 necropsies graded 3 and 4 was 9.4 per cent.[12]

Definite evidence of coronary atherosclerosis is the occurrence of obvious coronary insufficiency in coronary occlusion or angina pectoris. The important comparisons are made with these two entities where the atherosclerotic lesions in both instances are comparable. The presence of mild coronary atherosclerosis does not usually cause significant impairment of myocardial function, and results of necropsies indicate that coronary arteriosclerosis is apt to be out of proportion to clinical manifestations. It is possible that had there been more electrocardiograms in the studied group, more diagnoses of arteriosclerosis could have been made. However, at best, in the absence of a clinical history that indicates an impaired myocardium and inability to demonstrate conduction disturbances of the heart, the diagnosis of coronary arteriosclerosis from electrocardiographic evidence is difficult. It is the state of the myocardium and not that of the coronary arteries that is depicted by the electrocardiogram.[13]

This study was directed to the etiologic importance of cholesterol of nutritional origin in the genesis of atherosclerosis. Reference is made to the observations in experimental animals that have indicated hypercholesterolemia of nutritional origin to be a factor in the development of atherosclerosis. The relation of hypercholesterolemia, especially when associated with lipemia, to the increased incidence of atheromatosis in inherited and acquired endocrine disturbances in man is definite. The evidence presented from this investigation gives doubtful significance to the nutritional rôle of cholesterol in the genesis of human atherosclerosis. The nutritive imbalance as related to cholesterol in the experimental animal apparently produces some metabolic disturbance that has no similar significance in man, unless there is an associated endocrinopathy.

Summary and Conclusions

1. One hundred patients in the age period of 45 to 65 who had been subject to an abnormally prolonged increase of cholesterol in the diet were reviewed. The incidence of coronary arteriosclerosis as determined by the criteria used was no greater than in a control group.

2. The nutritional rôle of cholesterol in the genesis of human atherosclerosis is of doubtful significance unless there is an associated endocrinopathy.

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ELECTROCARDIOGRAPHIC STUDIES IN OLD AGE*

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One hundred and two men and women, 60 to 90 years of age inclusive, were studied electrocardiographically. These cases were chosen from a large group of inmates of a home for aged people. All men and women who had any complaints which may be interpreted as cardiovascular in nature were excluded from this study. None of these cases had a definite or equivocal history of heart disease. All our cases were ambulatory and not debilitated senile subjects. It is the purpose of this paper to present the results of this study.

There were 46 males and 56 females in the group. The largest number in either sex was between the ages of 70 to 79 and the smallest number was from 60 to 69. Actually a little over one-fifth of the cases were in the seventh decade, one-half of the cases in the eighth decade and one-third of the cases in the ninth decade (table 1).

Table I

Number of Cases Studied

Classified as to Age and Sex

Age Groups	60–69	70–79	80–90 and Over	Total
Males	8	22	16	46
Females	14	29	13	56
Total	22	51	29	102

Cardiac Rate. The average cardiac rate for the whole group was 82. Only eight cases presented a rate of 100 or more and no instance was found with a rate of less than 60 per minute. There was no variation in the cardiac rate from decade to decade. In the age group 70 to 79, and 80 to 89, the females showed a significantly higher cardiac rate than the males. The average for the females between 70 and 79 years of age was 84, and for the males in the same age group the average was 78. In the ninth decade, the average cardiac rate for females was 85 and for males 78. Although the average rate for the females was the same in all age groups, it was noted that more females had high cardiac rates in the 60 to 69 age group. In the male group the cardiac rate showed a definite decrease from the seventh to the ninth decade, both as to average rate and as to the number of patients with low rates (table 2).

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This study was made at the Brooklyn Hebrew Home and Hospital for the Aged.

TABLE II
Average Cardiac Rate

Age Groups	60–69	70–79	80–90+	Average
Males	84	78.2	76	79.4
Females	84	84	85.5	84.5
Average	84	81.1	80.7	81.9

Intervals. The average PR interval for the group was 0.180 second. The average QRS complex was 0.055 and was not found to differ much from group to group. The average QT interval was found to be .343 and slightly larger in the ninth decade. The average TP interval was found to be .250 and was the same in all age groups. No significant difference was observed in these intervals as between males and females (table 3).

TABLE III
Intervals

Age Groups	60–69	70–79	80–89	Average
PR	.18	.18	.19	.180
QRS	.055	.06	.06	.055
QT	.32	.34	.37	.343
TP	.26	.24	.26	.250

Axis Deviation. Our findings concur with the generally accepted observation that left axis deviation is common in older people. In our group of cases 76.6 per cent had left axis deviation and only 1.9 per cent had right axis deviation. Between the seventh and eighth decade there is a significant increase in the incidence of left axis deviation and from the eighth to the ninth decade there is only a slight increase. Eighty per cent of the females had left axis deviation as against 76 per cent of the male group (table 4).

TABLE IV
Axis Deviation

Age Groups	60–69	70–79	80–90+	Average
Left Axis	68.5%	78.5%	79.4%	76.6%
Right Axis	0	1.9	3.4	1.9

Conduction Disturbances. Almost 18 per cent of the whole group showed some conduction disturbance. It is of note that the incidence of disturbance in rhythm becomes greater as the age increases. In the 60 to 69 age group it was 9 per cent, and in the 80 to 90 age group it was 20.5 per cent. Auricular fibrillation and ventricular premature contractions were the most common findings. Nodal premature contractions were found in three cases. Auricular premature contractions and prolonged A–V conduction

were found in only two instances in each case. Left bundle branch block was found in two cases. It is of some significance to note that these two cases were both in the ninth decade. Auricular flutter was found in only one instance. Although the number of cases with conduction disturbance is too small to warrant any conclusions, it is quite obvious that the incidence of such disturbances is higher in the upper age group in our cases. It is also to be noted that ventricular conduction disturbance occurs more frequently in the older group (table 5).

TABLE V
Conduction Disturbance

Age Groups	60–69	70–79	80–90+	Percentage of Total
Number of Cases	22	51	29	
Auricular Premature Contraction		2		1.9
Nodal Premature Contraction	1		2	2.9
Ventricular Premature Contraction		2	2	3.9
Prolonged A–V Conduction		2		1.9
Auricular Fibrillation	1	3		3.9
Auricular Flutter		1		0.9
Left Bundle Branch Block			2	1.9
Number of Cases	2	10	6	
Percentage	9.1	19.6	20.6	17.6

*Evidence of Myocardial Damage.** An elevation or depression of the ST segment of more than 1 mm. occurring in any two leads was considered significant of myocardial disturbance. Inversion of the T wave in Lead I, II or IV and a deep Q wave in Lead I, III or IV were taken to mean myocardial damage. All cases with hypertension and marked left ventricular strain were excluded from this group.

It is of some interest to note that the electrocardiographic evidence of myocardial damage was found in nearly half of the cases (46.5 per cent). The highest incidence of such evidence was found in the eighth decade (58.9 per cent), and the lowest incidence was found in the ninth decade (37.9 per cent). This is particularly true in the males. The incidence of myocardial damage in males 60 to 69 years of age was found to be 50 per cent; 70 to 79 years of age, 59 per cent; and 80 to 89 years of age, 31 per cent. In the females the lowest incidence was found in the seventh decade (35.7 per cent) and the highest in the group of 70 to 79 years of age (58.9 per cent). It is of some significance to note that the electrocardiographic evidence of myocardial damage is found almost precisely as frequently in males as in females in the age group of 70 to 79 (table 6).

P Wave Changes. More than 50 per cent of our cases showed P wave changes. In the seventh decade this was found in 50 per cent of the cases;

*The criteria of the New York Heart Association were used in determining what constitutes evidence of myocardial damage. "Nomenclature and Criteria for Diagnosis of Diseases of the Heart," 4th Edition, New York Heart Association, 1939, New York.

TABLE VI

Electrocardiographic Evidence of Myocardial Damage

Age Group	60–69	70–79	80–90+	Average
Males	50.0%	59.0%	31.2%	47.8%
Females	35.7	58.9	46.1	50.0
Average	42.8	58.9	37.9	46.5

in the eighth decade in 45 per cent of the cases; and in the ninth decade in 65.5 per cent of the cases. The most frequent changes found were low voltage P_1 and negative P_4. Actually low P_1 was found in 20 cases and negative P_4 was found in 24 cases. Definite abnormalities, such as notched, widened, or high P waves, were found only occasionally.

QRS Changes. Almost one-third of our cases had changes in the QRS complexes. The most common change was notching of the QRS complex in the first lead. This common finding was observed in the upper two decades and not in the seventh decade. QRS changes are found more commonly in the male group than in the females. There is only a slight variation in the incidence of QRS changes from decade to decade (table 7).

TABLE VII

Abnormal Configurations

Percentage Incidence

	60–69	70–79	80–90	Average
QRS Complex	31.5	23.5	41.4	30.3
Initial Deflection (Q)	13.6	29.4	36.3	25.4
ST Interval	0	15.6	0	7.8
T Wave	27.2	15.2	31.0	23.5

Q Wave Changes. Twenty-five per cent of the group showed abnormal changes in the initial deflection. The largest number of changes was found in the fourth lead. In all age groups negative initial deflections were found in Lead IVF. It is noteworthy that the incidence of these abnormal deflections increases as age advances. In the seventh decade it was found only in 13.6 per cent, in the eighth decade it was found in 29.4 per cent, and in the ninth decade in 36.3 per cent. It is obvious that the incidence of abnormal deflections is almost three times as high in the ninth decade as in the seventh decade in our cases (table 7). It is of significance that with the advance in age negative initial deflections are found most commonly in the fourth lead. (We used IVF as our fourth lead.)

*ST Changes.** All our cases showing significant ST deviations were found in the eighth decade. Actually 15.6 per cent of this group showed deviations in the ST segment. No such abnormalities were observed in the

* All cases of hypertension and marked left or right ventricular strain were excluded from this study.

seventh and ninth decades (table 7). This finding becomes more significant when we consider the changes observed in the T wave in our group of cases.

T Wave Changes. Almost one-fourth of our cases showed abnormal T waves. These findings were most commonly observed in the ninth decade and least in the eighth decade. In the group 60 to 69 years of age 27.2 per cent showed abnormal T configurations. Only 15.2 per cent of the 70 to 79 year group showed such changes. Of the ninth decade almost one-third or 31 per cent showed significant T changes (table 7). Abnormal T changes were observed with the same frequency in the female group as in the male group. The most frequent finding in all groups was a negative T_4.

Comment

In recent years the aging process has been the subject of much study. The aging of the cardiovascular system has been considered as one of the primary underlying causes of senescence and death. Whether the evolution of diseases of the cardiovascular system is one of the processes of old age or a disease incident to old age is not the subject of discussion of this report. It is generally agreed that abnormalities of the cardiovascular tree are observed more frequently in the older age group than in younger individuals. Such abnormalities are manifested clinically by a variety of disability signs and symptoms. Occasionally considerable cardiac disease is observed in an otherwise symptom free individual. The observation that many old people have a sudden cardiac death from coronary disease without a previous history of cardiac disability has been made again and again by Aschoff [1] who believed that mere aging never results in deformation of the vascular wall and the vascular tube. In considering heart disease in the upper decades, it has been frequently suggested that the high morbidity and mortality from cardiovascular disease in these age groups is simply the end result of the effect of a long continuous contact of a deleterious agent with the organism; also that it takes the cardiovascular system many years to manifest its ability to cope with any damage received.

In the last few years some evidence is accruing to show that more damage can be demonstrated in the older age groups than is manifested by subjective symptoms. The electrocardiogram makes it possible to evaluate the integrity of the cardiac muscle and function in individuals who otherwise do not demonstrate any cardiac disability. It is generally demonstrated that the electrocardiogram is invariably altered where the integrity of the heart muscle or conduction mechanism is impaired.[2] Willius [3] studied the electrocardiogram in 700 people over the age of 74 and found abnormal tracings in more than 50 per cent of the cases. Gelman and Brown [4] showed abnormal electrocardiograms in 36 per cent of people above 61 years of age. Warnecke [5] showed that one-quarter of persons above the age of 70 had electrocardiograms indicative of myocardial disease, and Levitt [6] found the same incidence. In all these instances the cases studied were clinically

free of heart disease. In our study this is also the case. Our findings agree with those of Willius, namely that the incidence of definite electrocardiographic evidence of myocardial damage is found in nearly 50 per cent of people of the seventh, eighth and ninth decades. If these findings are compared with the electrocardiographic findings at the age of 40 (table 8), it becomes obvious that significant changes take place in the cardiogram in the aging heart.

TABLE VIII

Summary Table

Age Groups	60–69	70–79	80–90+	Total	40 Years* of Age
Number of Cases	22	51	29	102	
Average Rate	84	81.1	80.7	82	
Conduction Disturbance %	9.1	19.6	20.6	17.6	8.6
Auricular	4.5	15.6		8.6	4.1
Nodal	4.5	0	6.8	2.9	.4
Ventricular	0	4.5	13.6	5.8	4.1
Axis Deviation %					
Right	0	1.9	3.4	1.9	
Left	68.5	78.5	79.4	76.6	33.2
Myocardial Disturbance	42.8	58.9	37.9	46.5	
Q Wave	13.6	29.4	36.3	25.4	8.8
ST	0	15.6	0	7.8	1.1
T Wave	27.2	15.2	31.0	23.5	7.4

* Basic Studies of the Aging Cardiovascular System. Reproductions of charts shown in the scientific exhibit at the annual meeting of the American Medical Association, New York, June 10–14, 1940.—Metropolitan Life Insurance Company, New York City.

The electrocardiographic findings in our group of cases bring into view several points of interest. Electrocardiographic changes which are considered as definite evidence of heart muscle damage are found as frequently in females as in males. This finding is at variance with the common observation that degenerative heart disease is more common among males than females. If deviations in the electrocardiogram in the upper three decades of life, as presented here, are significant of definite heart muscle damage, one would be led to postulate from our observations that the incidence of subclinical heart disease in aged people is high. It would also seem reasonable to assume that females have a higher incidence of subclinical heart disease than do males. Do females in the older age groups have a greater aptitude to develop a collateral circulation, or do they develop degenerative heart disease later in life than males?

The second observation that one may make from our study is that electrocardiographic evidence of myocardial damage becomes more common as age advances. This is expressed in permanent deviations from the normal. Changes in the P wave, the QRS complexes, the T and Q waves are found more frequently with each advancing decade. Those changes, how-

ever, which are more functional in nature and possibly speak for transitory anoxemia of the heart muscle, are found less frequently in the upper decade. One is tempted to formulate the thought that as one grows older a new and adequate collateral coronary circulation develops as the old coronary tree sustains more and more damage.

Thus it may be said that changes in the electrocardiogram significant of definite heart damage may develop in the older age group of people in the absence of the usual signs and symptoms of coronary heart disease. It is plausible to assume from our observations that this subclinical form of degenerative processes of the coronary circulation is attended by the development of an adequate collateral circulation, thus increasing the functional life of the heart muscle. Are these changes a manifestation in the normal evolution of senescence of the cardiovascular system or the end result of a disease process?

Summary

1. One hundred and two men and women, 60 to 90 years of age, who presented no history or symptoms of cardiovascular disturbances, were studied electrocardiographically.

2. The findings were arranged in three age groups, 60 to 69, 70 to 79, and 80 to 90 years of age.

3. Three-quarters of the group had left axis deviation, and only 2 per cent showed a right axis deviation.

4. Conduction disturbances were found in 17.6 per cent of the cases. Abnormal conduction was noted more frequently in the older age group.

5. Nearly one-half of the cases showed definite evidence of myocardial damage. This evidence was found more commonly in the eighth decade than in any of the others and less commonly in the ninth decade. Abnormal deviation of the initial deflection and the T wave and abnormalities in the QRS complex were found more commonly as age advanced. Deviation of the ST segment, however, was found only in the eighth decade.

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ANEURYSM OF THE AORTA RUPTURING INTO THE RIGHT VENTRICLE *

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ANEURYSMS of the thoracic aorta are quite common; rupture into the right ventricle as herein reported is, however, of infrequent occurrence. Boyd [1] states that "0.1 to 0.5 per cent of deaths in American cities are due to aneurysms in the thorax." Lemann [2] noted aneurysms of the thoracic aorta in 0.3 per cent of all patients examined in a series of 2,000 autopsies. A similar incidence in postmortem studies was noted by Geraci [3] and by Ogden.[4] In these aneurysms, rupture occurred in from 39 per cent [5] to 52 per cent [1] of the cases reported. The more usual sites of rupture reported were: pericardium, left pleural cavity, esophagus, right pleural cavity, left bronchus, etc.[1]

Of interest are the ruptures into the superior vena cava [6] and pulmonary artery.[7]

Although Boyd gives the incidence of rupture of thoracic aorta aneurysms into the right ventricle as 1 per cent, in a review of the literature only three such cases occurring in acquired aneurysms were found.

The first is that of Laycock [8] who reported the case of a 56 year old man who had extensive syphilitic disease of the aorta with a fusiform aneurysm of the ascending portion of the aorta from which a small sac had budded off and ruptured into the conus arteriosus of the right ventricle. This man's symptoms were of four months' duration. Death was due to cardiac failure.

The second is that of Lichtenburg [9] who, in 1865, recorded the case of a 29 year old male who died of heart failure 14 days after the onset of symptoms. The aneurysm here was small. It arose from the aorta at a site behind the "posterior semilunar valve" and bulged into the right auriculoventricular opening, and at one point had ruptured into the right ventricle.

The third case is more recent. It was reported by Schwab and Sanders [10] in 1931. This patient was a 28 year old colored male, who had a tremendous saccular aneurysm of the ascending portion and arch of the aorta; there was also a small aneurysm arising behind the "right posterior" cusp of the aortic valve, extending down behind the pulmonary artery and rupturing through one of the leaflets of the pulmonary artery into the right ventricle. The edges of the ruptured area were rounded and smooth; it was thought to have been present for some time. Suggestive symptoms had been present for two months.

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There is another case recorded by Tompkins [11] in which an aneurysm of one of the sinuses of Valsalva ruptured into the right ventricle. This report was not available and so the etiology here could not be determined.

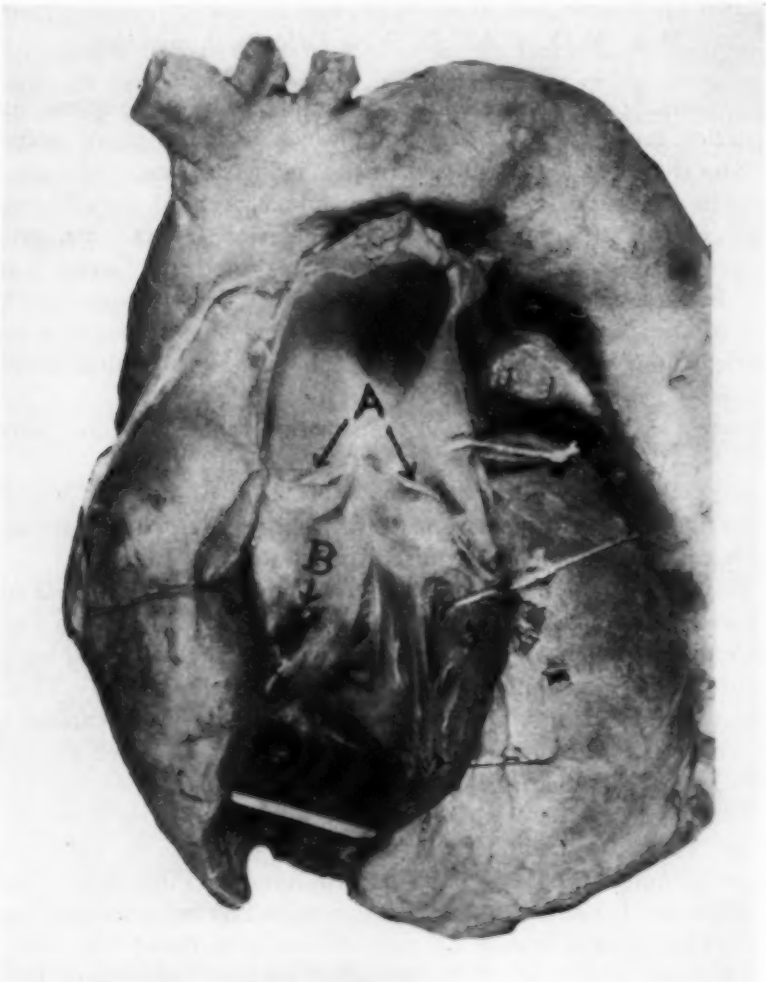

FIG. 1. The right ventricle and pulmonary artery have been opened. Pulmonary valve leaflets shown at A. Site of rupture of aneurysm into right ventricle through posterior wall is shown at B.

CASE REPORT

The patient was a 61 year old colored male who came to the hospital for the first time in January, 1940, complaining of a painless mass on his left arm. This mass had been present for 12 years, during which time it was gradually increasing in size. The patient had no complaint referable to the cardiorespiratory system at that time. On examination, the mass on the left arm was considered to be a lipoma. The patient's blood pressure was 160 mm. Hg systolic and 100 mm. diastolic. There were

no abnormal physical findings referable to the heart or lungs. An electrocardiogram on January 19, 1940 reported evidence of left axis deviation and definite myocardial disease. Urinalysis on that admission was negative. Blood Kline and Kolmer tests were strongly positive. Under local anesthesia, the lipoma of the left arm was removed. The patient's postoperative course was uneventful and he was discharged about two and one-half weeks after admission.

He returned to the hospital on April 10, 1942 with the complaint of dyspnea and retrosternal pain. Dyspnea had been present for about one year prior to this time,

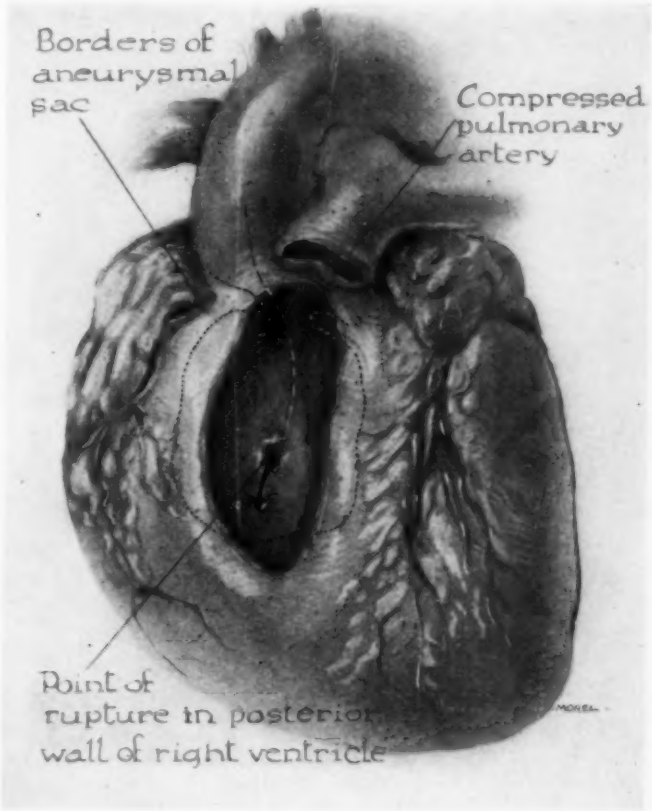

FIG. 2. Half-tone drawing of heart and large vessels. Portion of anterior wall of right ventricle removed to show tear in the posterior wall. Arrow indicates communication between aneurysm of aorta and right ventricular cavity. Dotted lines represent borders of aneurysm extending into posterior wall of right ventricle.

and had gradually progressed almost to orthopnea. The retrosternal pain was present also for about a year. It had been noted particularly on exertion. Gradually, however, it had become a persistent dull ache and for the month prior to admission, paroxysmally, it would become severe and tearing in character. The past history indicated that the patient thought he had had rheumatic fever when a boy.

On examination on April 10, 1942, the temperature was 98.6° F., pulse 95, respirations 25, and blood pressure 110 mm. Hg systolic and 40 mm. diastolic. The patient was a well-developed, well-nourished colored male, who was moderately dyspneic. The pupils reacted to light. There was a tracheal tug and the neck veins

pulsated visibly. Some basal râles were present over the lung fields. The heart was enlarged downward and to the left. There was an expansile pulsation in the third left interspace. In this same area, harsh systolic and diastolic murmurs were heard. These murmurs were also heard to a lesser extent over the entire precordium. The liver was palpable two fingers'-breadth below the right costal margin. Traube's and Duroziez's signs and a Corrigan pulse were elicited over the peripheral vessels. Deep reflexes were equal and active.

FIG. 3. Gross photograph, inner aspect of aorta, showing opening into sac of aneurysm at A, 3 cm. distal to aortic valve at B.

Urinalysis on April 11, 1942 showed albumin (+) and occasional white blood cells on microscopic examination. Blood Kline and Kolmer tests were again positive on this admission.

The patient's condition remained unchanged until the morning of April 13, 1942. At this time, he suddenly experienced great weakness. Retrosternal pain was accentuated. He became cold and the pulse was scarcely perceptible. Heart sounds were distant; the murmurs were still heard, but no notation of change in these murmurs was mentioned in the record. It had been considered that aortic aneurysm was present and that now rupture had occurred. The possibility of rupture into the pulmonary artery was entertained. The patient died within three hours after this sudden collapse.

Necropsy. At autopsy, the most important findings were noted in the chest. The visceral and parietal layers of the pericardium were adherent to one another over the upper anterior aspect of the right ventricle and the anterior portion of the beginning of the aorta. An abnormal bulge was present in this area. On opening the right ventricle, the bulge was seen to extend down from the aorta into the posterior aspect of the right ventricle. On the posterior wall of this structure in the conus arteriosus, below and to the right of the pulmonary valve was an irregularly roughened opening, measuring about 5 by 3 mm. (figure 1). An area about this opening measuring about 1.5 cm. in diameter, was reddened, thin and friable. On opening the aorta, it was found that this hole in the posterior wall of the right ventricle communicated with a saccular aneurysm of the aorta (figure 2). This

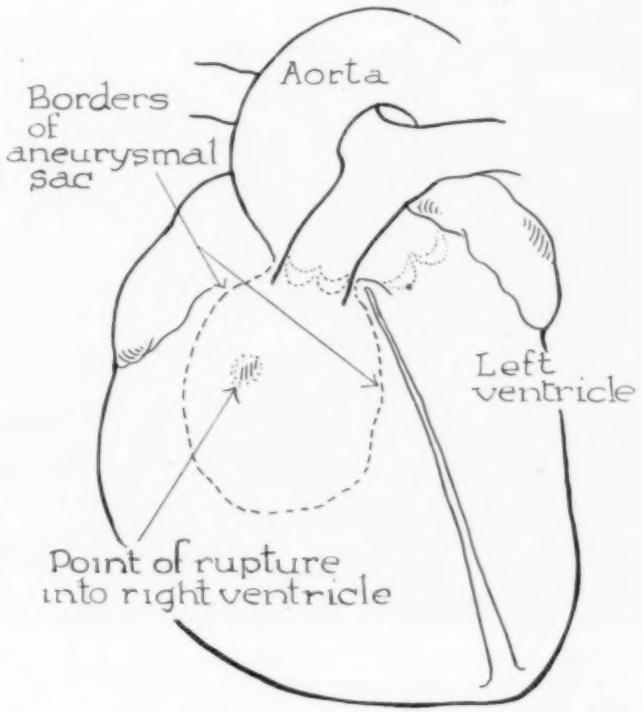

FIG. 4. Diagram to show relationship of aneurysm to interventricular septum and the pulmonic and aortic valves. The extent of the aneurysm and its origin from the proximal portion of the aorta is shown by the dotted line.

aneurysm arose through an orifice in the anterior right lateral aspect of the aortic wall, about 3 cm. above the aortic valve cusps (figure 3). The orifice measured 3.5 cm. in diameter. The sac into which the orifice led measured about 6 cm. in diameter. It bulged anteriorly and downward into the posterior aspect of the conus arteriosus of the right ventricle (figure 4). There was much dense reactionary fibrous tissue in the areas adjacent to the sac wall. The free borders of the aortic cusps were somewhat rolled. The ostium of the left coronary artery was definitely narrowed. The ostium and first several centimeters of the right coronary artery could not be identified. A small dimpled area in the region of the right anterior aortic cusp was thought to represent the completely occluded ostium of this artery. The aneurysm was so situated as to press on the pulmonary artery at its valve and main trunk. In addition to this large saccular aneurysm, there were smaller localized outpouchings

below it, in each of the sinuses of Valsalva. The inner surface of the aorta and of the aneurysms showed very pronounced "tree-bark" wrinkling, indicative of syphilis, and some elevated pearly gray and yellow plaques. Calcium deposits were present in the wall of the aorta and the large aneurysmal sac. The heart weighed 560 grams. The myocardium of both right and left ventricles, especially the former, was firm and hypertrophied, measuring 1 cm. and 2 cm. respectively, in thickness. Both the right auricle and right ventricle were markedly dilated.

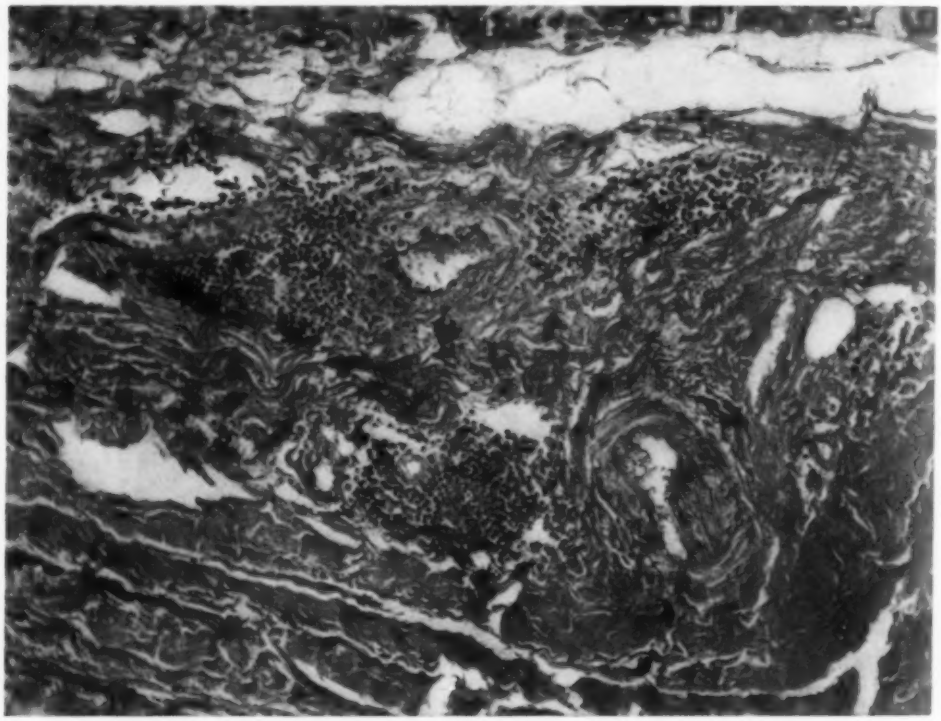

FIG. 5. Photomicrograph of section from aortic wall showing perivascular collections of plasma cells and lymphocytes. Endarteritis and thickening of wall of vasa vasorum with narrowing of lumen is shown.

The lungs, liver, and spleen showed no definite gross abnormality. The kidneys each weighed about 160 grams. They had quite adherent capsules, and granular and pitted cortical surfaces.

Microscopically, very marked perivascular lymphocytic infiltrations and endarteritis of the vasa vasorum were noted in sections of the aorta. Large lymphocytic collections were also present in the media of the aorta (figure 5). Some hypertrophy of myocardial fibers was noted. Lymphocytes were abundant in the epicardium. Kidney sections showed interstitial fibrosis, lymphocytic infiltration, thickened medullary and pelvic structures, fibrosed glomeruli, and "colloid" casts in the tubules. The lungs, liver and spleen showed microscopic evidence of passive congestion.

Pathologic Diagnosis. Aneurysms of the aorta (intrapericardial portion and sinuses of Valsalva) with rupture into the right ventricle. Cardiac hypertrophy and dilatation. Syphilitic aortitis. Chronic pyelonephritis. Passive congestion of lungs, liver and spleen.

Discussion

Etiology. In the case herein reported, as well as in the cases of Laycock, Lichtenburg, and Schwab and Sanders, the causative disease was syphilis. The complication of communication between the aorta and the right ventricle, however, need not be on a syphilitic basis. Congenital aneurysms of the aorta, especially of one or all of the sinuses of Valsalva, have been recorded by Abbott,[12] Micks,[13] and others.

The communication may be established on a mycotic basis, as in bacterial endocarditis or endarteritis.[14] Arteriosclerotic disease of the aorta has also been considered as a possible causative agent.

Location. Aneurysms of the intrapericardial segment of the aorta may be just above the sinuses of Valsalva, or they may actually involve one or all of the sinuses. In our case, the largest aneurysm was the saccular one which arose some 3 to 4 cm. above the aortic valve cusps. Smaller aneurysms were also present in each of the sinuses. Ostrum et al.[15] noted four cases of aneurysm of the sinuses of Valsalva in 3,000 autopsies. According to Snyder and Hunter,[16] aneurysms of the sinuses of Valsalva constituted 0.93 per cent of aortic aneurysms in a series of 5,896 autopsies. Rupture of syphilitic aneurysm of a sinus of Valsalva into the right auricle is recorded by Wright [17] and by Higgins.[18]

Since the right coronary artery could not be identified in this case, the possibility that the aneurysm here may actually have taken origin from or, at least, bulged into this vessel was suggested. Syphilitic aneurysms of coronary arteries do occur.[16, 19] In our case, however, the orifice of the aneurysmal sac was definitely above the site of the ostium of the right coronary. A dimpled area in the right anterior sinus of Valsalva is believed to represent the occluded right coronary ostium.

From the standpoint of proximity, aneurysms of the heart should also be mentioned. Most cardiac aneurysms, of course, follow myocardial infarction and are situated at the anterior or lateral part of the apex of the left ventricle.[20, 21, 22, 23] Aronstein and Neuman,[24] however, report a case and collected 11 others undoubtedly syphilitic in origin. These may be near the base of the heart, due to gummata, or they may be more in the apical portions usually due to a more diffuse syphilitic myocarditis. The aneurysm herein reported was definitely not cardiac in origin, as noted by its location. Its intimate relationship with the heart was due to the usual course along which it eroded.

Effects of Aneurysms at This Site. 1. Garvin and Siegel [25] have discussed the cor pulmonale resulting from obstruction of the pulmonary artery from pressure of a syphilitic aortic aneurysm. Dickens [26] presented a case in which an aortic aneurysm located just above the right and left anterior cusps protruded into the pulmonary artery and right ventricle, the combined pressure and anatomic distortion causing stenosis of the right pulmonary artery. Here also the sac distorted the right posterior cusp of the pulmonary

valve leading probably to an insufficiency of this valve. Cor pulmonale and death due to congestive failure occurred. In our case, the right ventricle and auricle were notably hypertrophied and dilated and undoubtedly an effective pulmonary stenosis and possibly an insufficiency were present during life. These findings suggest an explanation for the murmurs heard clinically.

2. In Schuster's case [19] of aneurysm of the sinus of Valsalva, the coronary orifice was involved by pressure and the patient had symptoms of angina pectoris. Apparently in the case herein reported, the right coronary artery was completely occluded by the gradual pressure and reactionary fibrosis due to the advancing aneurysmal sac. It may well have been, therefore, that the patient's complaint of retrosternal pain was on this basis. This effect on the coronaries is a mechanical one and is independent of, though synergistic with, the classical syphilitic narrowing of the coronary ostia. This latter lesion was, of course, also present in our case.

3. Crawford and De Veer [27] described a case of aneurysm of the aorta, arising just above the aortic valve, protruding into the right ventricle with damage to the interventricular septum. This patient clinically had electrocardiographic evidence of partial right bundle-branch block. He lived 11 months after this diagnosis was made. Heart block or bundle-branch block is, therefore, another possible effect of these aneurysms. Whether such was a factor in our case cannot be definitely stated. Though anatomically possible, the location of the aneurysm here appears to make it less likely. If any part of the conducting mechanism was involved, the right bundle branch would be most plausible.

4. The last effect of these aneurysms to be discussed is rupture. The incidence and sites of rupture have already been considered. Although in one of the cases of rupture into the right ventricle [10] it was definitely stated that the communication between aorta and right ventricle had been present "for some time" (possibly two months), this appears to be the exception. Most such cases die shortly after rupture occurs. In our case, judging from the irregular margin of the rupture site coördinated with the clinical story of sudden collapse shortly before death, it is believed that rupture was the terminal happening probably three hours before the patient died (clinical). Should a patient with such a pathological lesion survive for some time, the diagnosis of Maladie de Roger, which was made in the case of Schwab and Sanders,[10] is certainly understandable.

Summary

Rupture of syphilitic aneurysms of the aorta into the right ventricle is of rather rare occurrence. A case showing this complication is reported, and three other cases from the literature are alluded to. Aneurysms of the intrapericardial portion of the aorta may be on a syphilitic basis, or they may be congenital, mycotic, or arteriosclerotic in origin. In differentiating aneurysms in this locality, those arising from the sinuses of Valsalva, from the

coronary arteries, or from the heart itself are considered. The possible effects produced by these dilatations are: cor pulmonale due to pulmonary stenosis with or without insufficiency; pressure on the coronary arteries with changes due to coronary insufficiency; pressure on the conducting mechanism of the heart with heart block or bundle-branch block; and rupture of the aneurysms, usually fatal within a short period of time.

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THE SOURCE OF SULFATHIAZOLE HEMATURIA INDUCED IN RABBITS *

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It is known that sulfonamide drug therapy may be complicated by the precipitation of crystals or the formation of concretions in the urinary tract. Considerable evidence has been presented indicating that these crystals may be responsible for the anuria, azotemia and hematuria encountered during sulfonamide therapy. The possibility that these drugs may induce hematuria through some toxic action on the glomeruli has not been excluded.

It seemed advisable to determine the source of hematuria in experimental animals and to establish the relative frequency of these two potential sources. At autopsy glomerular bleeding would be indicated by the presence of red blood cells in Bowman's capsules or in the renal tubules. The absence of these microscopic changes would suggest an extraglomerular source of the hematuria.

Since sulfathiazole was used in the experiments to be described in this paper, the literature concerning this drug is here emphasized. Data on other sulfonamides are included only when considered by other authors. In the literature descriptions of the extrarenal portion of the urinary tract are often lacking. Such reports are omitted.

Literature

Cooper, Gross and Lewis [1] first noted that sulfathiazole, like sulfapyridine, produced renal concretions in rats. Rake et al.[2] first observed hematuria in mice receiving sulfathiazole. Rake et al.[3] described the pathological changes noted after prolonged administration of sulfapyridine and sulfathiazole to mice, rats, and monkeys. Of 52 mice on sulfathiazole, blood was present in Bowman's capsules and in the convoluted tubules of two. These changes were not present in the mice on sulfapyridine. Thirty-six rats received sulfapyridine, and the renal tubules of one contained blood. The kidneys of the rats on sulfathiazole were free of blood. Of seven monkeys on sulfathiazole, one developed hematuria, but the renal tubules of this animal were free of blood. All three monkeys on sulfapyridine for 14 days showed evidence of glomerular bleeding. However, four monkeys which received an equivalent dose of sulfapyridine for 21 days did not have

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† Winthrop Chemical Company Fellow; deceased May 4, 1944.

these renal changes, although hematuria had been observed in two of them. These data made the authors state: "Besides those renal changes due to the mechanical effect of the crystals or of concretions of these crystals, there appeared to be primary damage to the glomeruli. . . ." The different effects noted in the test animals were attributed to variation in species susceptibility.

Marshall et al.[4] found occasional red cells in the collecting tubules of rabbits given sulfathiazole, sulfaguanidine, or sulfapyridine. Bowman's capsules were free of blood. Climenko and Wright[5] describe the effect on monkeys of continued administration of sulfathiazole and sulfapyridine. Hematuria was noted in five of the 16 animals on sulfathiazole. A review of their protocols indicates that the blood in the urine of four of these animals arose from hemorrhages which were found in the renal pelves, ureters, or bladder. There was no evidence of glomerular hemorrhage in the remaining animal. Kolmer[6] administered sulfathiazole orally to 12 rabbits in doses ranging from 0.05 to 0.20 gm. per kilogram. In one animal blood was found in the capsules of Bowman. Similar changes were found twice in a corresponding series of rabbits receiving sulfathiazoline.

Only a few autopsies have been reported on patients who developed hematuria from sulfathiazole. In some of the reported cases details pertinent to our problem are not given; others are complicated by the presence of renal lesions unrelated to drug therapy. The authors are quoted to avoid interpretation of their descriptions.

Pepper and Horack[7]: "The renal pyramids were large and contained small hemorrhages . . . and streaks of crystalline material." . . . "The pelves were grossly hemorrhagic and contained deposits of gritty sand-like material." "Ureters were negative." "Bladder mucosa was reddened." "There was . . . a mild degree of benign nephrosclerosis." "There was fresh hemorrhage into and about the collecting tubules." The subepithelial connective tissue was intensely congested and hemorrhagic.

Burch and Winsor[8]: Case 1. "The urinary bladder was congested and hemorrhagic, being most marked in the region of the trigone." No reference is made to red cells in the renal tubules. Case 2. Had cardiac enlargement and probably hypertension. Autopsy showed polycystic kidneys. "There was extreme medial thickening of the arterioles and interlobular arteries. The tubules were markedly dilated and were filled with polymorphonuclear cells and erythrocytes."

Lindner and Atcheson[9] describe in two patients the presence of hemorrhage into the renal parenchyma as well as into the mucosa of the pelves and ureters. However, the incomplete description of microscopic findings limits the value of their cases.

Winsor and Burch[10]: Case 1. "The bladder contained numerous submucosal hemorrhagic areas in the region of the trigone." No red cells are described in the renal tubules or in Bowman's capsules. Case 2. "The left

ureter was dilated and congested, and its lumen contained a plug of crystals. . . ." "The capillaries (in the kidney) were congested and an occasional intertubular hemorrhage from the vessels was noted." Case 3. Died 21 days after the onset of hematuria. No source was apparent at autopsy.

Simon and Kaufman [11]: "The renal pelvis . . . showed a few bright red, punctate hemorrhages less than 1 mm. in diameter. No crystals were present." The glomeruli "showed marked hyperaemia of the capillaries and the presence of considerable amounts of albuminous material within the subcapsular spaces." No erythrocytes were described in the tubules.

Luetscher and Blackman [12]: Case 1. In addition to extensive renal tubular injury, red cells were present in a rare cortical tubule, and segments of the basement membranes of the glomerular capillaries were thickened and hyaline. A good many of the interlobular veins were filled with organizing thrombi, and there were tubulo-venous communications. The pathogenesis of the hemorrhages just described is not clear enough to be of value in this paper.

Materials and Methods

Normal adult rabbits of both sexes weighing between 1.8 and 2.2 kilograms were used. Animals 18 to 36 inclusive were from a pure Chinchilla strain. The remaining rabbits were from inbred stock. Some of the animals were fed "Domino all-in-one Rab-ets" *; the others received oats. Water was available throughout the period of observation.

As separate metabolism cages were used, individual urine specimens were obtained. These were strained to separate fecal material and preserved in toluene for analysis the next morning. The pH, protein content and character of the centrifuged sediment were recorded routinely. Before and after giving sulfathiazole, there was a crystalline precipitate in the urine which interfered with the microscopic examination. The following symbols were used as a rough expression of the amount of hematuria: 1 +, 2 + and 3 + respectively, indicated the presence of less than one, several, and many red blood cells per high power field; 4 + signified gross hematuria; 0, the absence of red blood cells. In the sediment drug crystals were almost always present after treatment. Alkacid test paper ** and the nitric acid test were employed for the pH and protein determinations.

A measured amount of powdered sulfathiazole *** was suspended in 50 c.c. of water. This was administered by stomach tube and carefully washed down with 100 c.c. of water. Animals which were killed were promptly autopsied; the others as soon as possible. At autopsy particular attention was paid to the urinary tract, and microscopic sections, from one to three blocks of each kidney, were made. The tissues were fixed in Zenker-

* Vitality Mills, Inc., Chicago, Illinois.
** Fisher Scientific Company, Pittsburgh, Pennsylvania.
*** Furnished by the Calco Chemical Division, American Cyanamid Company, Bound Brook, New Jersey.

formalin, and stained with hematoxylin and eosin. Blood levels of sulfathiazole were determined by the method of Bratton and Marshall,[13] a blank being run on the blood of each rabbit. Non-protein nitrogen was determined by the method of Folin and Wu.

Procedure

Once the animals had adapted themselves to their new environment and diet, daily urines were examined during a control period of two to six days. In only one instance (animal 27) were abnormalities noted before treatment, and this animal was discarded. The drug was given as previously described and the urinary findings recorded. At various intervals after the appearance of hematuria autopsies were performed, and the source of the hematuria determined.

Results

The experimental data are listed on the chart. It is to be noted that an adequate extrarenal source of the hematuria was found during the gross examination of every animal that developed hematuria. In most instances several hemorrhages were noted. These were usually located in the ureters, less frequently in the pelves, and occasionally in the bladder. Animal 25 was the only one to develop hematuria in which gross hemorrhage was not present, and in this animal two tiny ulcers were found in one ureter. These could explain the inconstant rare red cell observed in the urine, although it is also possible that we overlooked a tiny hemorrhage. No hemorrhages were found in the urinary tracts of the rabbits which did not develop hematuria (Nos. 21 and 22, and the controls).

There was no microscopic evidence to indicate that the hematuria induced by sulfathiazole arose from the glomeruli. The glomerular capillaries of the treated animals resembled those of the controls. The presence of a few erythrocytes in the terminal collecting tubules of four (Nos. 21, 25, 26 and 42) of the 22 treated animals was not considered a manifestation of glomerular damage by sulfathiazole, because similar collections were present in the tubules of seven (Nos. 29, 33, 34, 36, 49, 50 and 54) of our 14 controls. The exact significance of these red blood cells is not apparent. They were found only in a few of the terminal collecting tubules near the tip of the pyramid. It is possible that they escaped from glomeruli injured by a chronic focal renal disease present in several of the control and treated animals. Perhaps they were introduced during the cutting of blocks at autopsy. It seems likely that similar groups of red cells have been described previously [4, 6] in rabbits treated with the sulfonamides.

Some of the untreated animals were fed Rab-ets, the others oats. Six (Nos. 49 to 54 inclusive) of the 14 controls were gavaged for five successive days with 100 c.c. of tap water. With one exception, the urinary tracts of

TABLE I

The Source of Sulfathiazole Hematuria Induced in Rabbits

Animal Number	Diet	Reaction of Urine	Sulfathiazole Dosage	Hematuria—Amount* and Day of Appearance after 1st Dose Days												Blood Chemistry at Autopsy			Location of Hemorrhages Found at Autopsy	Evidence of Glomerular Bleeding due to Sulfathiazole
				1	2	3	4	5	6	7	8	9	10	11	12	NPN mg. %	Sulfathiazole			
																	Free mg. %	Total mg. %		
18	Rabbits	Basic	1.5 gm.-6 days 6.0 gm.-5 days	0	0	0	0	0	0	0	0	0	0	d† 4+			115	165	Several, 1–2 mm., right pelvis	None
19	Rabbits	Basic	1.5 gm.-6 days 6.0 gm.-6 days	0	0	0	0	0	0	0	0	0	0	2+	k† 4+	220	43	79	One minute, bladder. Many tiny, left ureter	None
20	Rabbits	Basic	1.5 gm.-6 days 6.0 gm.-4 days	0	0	0	0	0	0	0	0	0	d 2+				90	130	Several minute, left ureter; small groups, left pelvis	None
21	Rabbits	Basic	2.0 gm.-6 days	0	0	0	0	0	k								0.3	1.7	None found	None‡
22	Rabbits	Basic	2.0 gm.-6 days	0	0	0	0	0	k								0.3	2.1	None found	None
23	Oats	Acid	2.0 gm.-2 days	1+	d 4+											152	6.6	67	Interstitial hemorrhage, both kidneys. Many small hemorrhages, ureters and pelves	None
24	Oats	Acid	2.0 gm.-3 days	1+	0	k 4+										100	17	60	Two tiny, bladder; few right ureter	None
25	Oats	Acid	2.0 gm.-3 days	0	1+	0	k 1+									45	0.4	0.5	Tiny ulcer, right ureter and pelvis. No gross hemorrhage	None‡

TABLE I—*Continued*

Animal Number	Diet	Reaction of Urine	Sulfathiazole Dosage	Hematuria—Amount* and Day of Appearance after 1st Dose Days												Blood Chemistry at Autopsy			Location of Hemorrhages Found at Autopsy	Evidence of Glomerular Bleeding due to Sulfathiazole
				1	2	3	4	5	6	7	8	9	10	11	12	NPN mg. %	Sulfathiazole			
																	Free mg. %	Total mg. %		
26	Oats	Acid	1.5 gm.-3 days	1+	2+	k 2+										41	3.8	9.4	Two minute, bladder	None‡
28	Oats	Acid	1.5 gm.-4 days	0	2+	2+	k 4+									52			Crystals, hemorrhages and clot, left ureter	None
29 to 36	Controls			See text															None found	None‡
37	Oats	Acid	2.3 gm.-5 days	0		2+		k 4+									18	73	Few petechial, right ureter and both pelves	None
38	Oats	Acid	2.3 gm.-4 days	0	2+	2+	k 4+									144	6.3	87	Few minute, both ureters and bladder. Rt. obstructed by crystals and bloody fluid	None
39	Oats	Acid	2.0 gm.-8 days	0	0	0	0	0	0	0	k 4+					48	1.6	9.8	Right hemoureter. Minute hemorrhages, ureter and pelvis	None
40	Oats	Acid	2.0 gm.-1 day	4+	k											76	2.5	15	Upper 2 cm rt. ureter occluded by crystals and clot. Small hemorrhages underneath. Left hemoureter above crystalline obstruction at bladder. Hemorrhages in mucosa	None
41	Oats	Acid	2.0 gm.-5 days	0	0	0		k 4+								148	12	51	Several small, both ureters	None

TABLE I—*Continued*

Animal Number	Diet	Reaction of Urine	Sulfathiazole Dosage	Hematuria—Amount* and Day of Appearance after 1st Dose Days												Blood Chemistry at Autopsy			Location of Hemorrhages Found at Autopsy	Evidence of Glomerular Bleeding due to Sulfathiazole
				1	2	3	4	5	6	7	8	9	10	11	12	NPN mg. %	Sulfathiazole			
																	Free mg. %	Total mg. %		
42	Oats	Acid	2.4 gm.-days 1 and 5	0				1+	k 3+							55	5.3	12	Many confluent, upper rt. ureter; wall edematous, hyperemic	None‡
43	Oats	Acid	2.0 gm.-day 1 1.5 gm.-day 5	0				1+	k 0							216	2.4	8.5	Few minute, ureters and pelves	None
44	Oats	Acid	2.1 gm.-days 1, 2, 4 and 5	0	0	0	0	1+	k							58	11	15	One minute, in bladder	None
45	Oats	Acid	2.3 gm.-2 days	0	1+	k 4+											4.6	57	Bilateral hemoureter above crystalline obstructions at bladder. Many in mucosa	None
46	Oats	Acid	2.3 gm.-2 days	0	2+	k 4+										78	6.8	34	Left ureter dilated and hyperemic. Hemorrhages in pelvis	None
47	Oats	Acid	2.3 gm.-2 days	0	4+	k 4+										136	4.0	62	Massive crystalline deposits in pelves over a few hemorrhages	None
48	Oats	Acid	2.2 gm.-1 day	2+	k 4+											74	3.6	30	Several, both pelves; few, right ureter	None
49 to 54	Controls		See text																None found	None‡

* Amount of Hematuria
0 = no hematuria
1+ = less than 1 RBC per h.p.f.
2+ = several RBC per h.p.f.
3+ = many RBC per h.p.f.
4+ = gross hematuria
Vacant space indicates urinalysis not recorded for that day

† k = killed d = died
‡ A few RBC were found in the terminal collecting tubules of 4 of the 22 treated animals and 7 of the 14 controls. See text.

those animals were normal. Animal 52 had lesions typical of acute, diffuse hemorrhagic nephritis.

An observation of clinical interest is that most of the treated animals developed azotemia as well as hematuria. The coexistence of these two toxic manifestations has been observed frequently in man. This finding re-emphasizes the need for tests of renal function in those patients who develop hematuria. Of academic interest is the demonstration that it is possible to induce hematuria in a high percentage of rabbits when large doses of sulfathiazole are given.

The first five animals (Nos. 18 to 22 inclusive) were fed Rab-ets. Larger doses of sulfathiazole and a longer period of time were required to induce hematuria in them than in the animals that received oats. This variation in tolerance was associated with a difference in the pH of the urine. Animals fed Rab-ets excreted urine with pH ranging around 8, whereas the urine of animals on an oat diet was acid, pH 4 to 6. It is known that the solubility of sulfathiazole and acetylsulfathiazole is greater in alkaline than in acid urine.[14, 15]

Discussion

It has been shown that the hematuria which was experimentally induced in 20 rabbits by the administration of sulfathiazole arose from hemorrhages in the renal pelves, ureters, or bladder. The apparent explanation of these hemorrhages is trauma from the precipitated drug crystals. In support of this hypothesis crystals were frequently seen penetrating the mucosa at the site of hemorrhage. A photomicrograph shows one such area. In many other instances a collection of crystals was closely adherent to the hemorrhagic area.

In the routine sections of other organs were found several instances of arteritis and periarteritis. Our data are too limited to indicate whether or not this was a direct reaction to the drug. Rich,[16] however, has presented evidence indicating that lesions characteristic of periarteritis nodosa may be produced in man by hypersensitivity to sulfathiazole. Such lesions affecting the glomeruli would permit the extravasation of blood. It is also conceivable that hematuria could be produced by the focal necrosis described by Merkel and Crawford[17] or by the mechanical action of crystals on the renal tubules. None of these sources for hematuria was observed during this experiment.

Most of the reports found in the literature are in full agreement with those here reported. It is likely, therefore, that the hematuria induced in animals and man by the administration of sulfathiazole is usually extraglomerular in origin. Apparently hematuria from sulfapyridine[18, 19] and sulfadiazine[20] may have a similar source. Differences of opinion exist concerning the possibility of direct glomerular injury by sulfathiazole. This contingency is extremely difficult to exclude. However, the lack of suitable

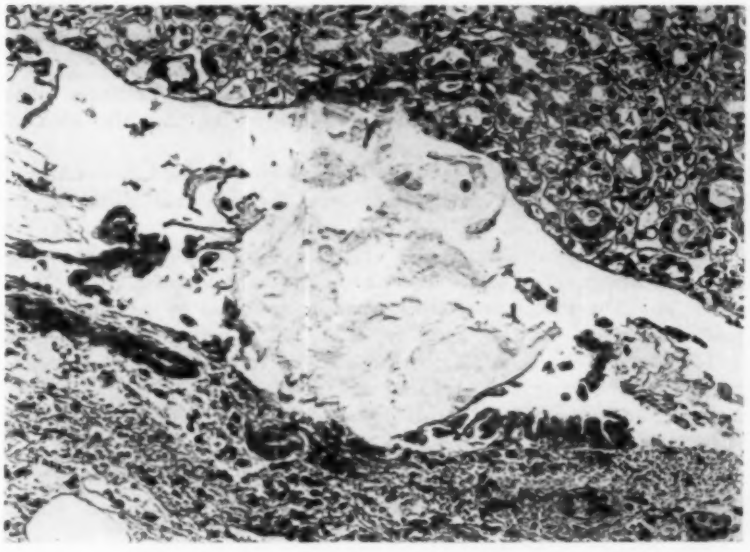

FIG. 1. Photomicrograph × 200. Renal pelvis and pyramid. Rabbit No. 27. The epithelium is ulcerated and penetrated by a mass of sulfathiazole crystals. There is hemorrhage in the submucosa.

controls in previous animal experiments and the presence of co-existing disease in man weaken the reported evidence for direct glomerular injury by sulfathiazole.

SUMMARY

Hematuria was induced in 20 rabbits by the peroral administration of sulfathiazole. With one possible exception, adequate source for the blood was found in hemorrhages located in the renal pelves, ureters, or bladder. A few large, collecting tubules in four of the 22 treated animals and in seven of the 14 controls contained a few red blood cells. In none of the kidneys was there any evidence to indicate that sulfathiazole had injured the glomeruli. Rabbits having an alkaline urine from eating Rab-ets developed hematuria from sulfathiazole less readily than did the animals with an acid urine from oats.

CONCLUSIONS

The hematuria experimentally induced in rabbits by sulfathiazole was extraglomerular in origin.

We wish to acknowledge our appreciation of the assistance given by Dr. E. K. Marshall, Jr.

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CASE REPORTS

THE COEXISTENCE OF TOPHACEOUS GOUT AND NONTROPICAL SPRUE. REPORT OF A CASE*

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We recently observed a case wherein severe tophaceous gout coexisted with nontropical sprue. We were unable to find a record of a similar case after careful search of the literature.

Case Report

A 50 year old man registered at the Mayo Clinic in August, 1939, complaining of loss of weight, intractable diarrhea and recurrent attacks of severe arthritis. He had spent all of his life in Canada except for rare, brief visits to the northeastern part of the United States. He smoked approximately 20 cigarettes each week. He used alcohol only as an occasional social cocktail.

For at least 25 years, he had had two or three soft, semiformed stools daily. He had attached no particular significance to this and had believed that it was normal for him. During this time, he had noted that for intervals of seven to 10 days, for no accountable reason, the stools had become more frequent and had occurred approximately six times daily. The stools always had been bulky, foamy, frothy, light in color, foul in odor, and shiny and greasy in appearance, which had suggested an excessive amount of oil. Many of the stools had been watery, and there had been a considerable degree of associated flatulence. Some of the bowel movements had been so bulky that the patient had estimated that they were from one to two pints (1,000 c.c.) in size. For a year and a half before the patient came to the clinic, the diarrhea had been protracted and unremitting and he had lost about 35 pounds (15.9 kg.).

Three years previously, without apparent provocation, he had experienced a sudden painful swelling of the joint of the great toe of the left foot. The joint had been red and so tender that he had not been able to put weight on it. The affected part had been put at rest and heat had been applied. The symptoms had subsided in approximately 10 days without any residual distress or limitation of motion. One year later, a similar involvement of the great toe on the right foot had occurred. This attack had lasted approximately two weeks and then had subsided without any residuum. Six months before the patient registered at the clinic, he had had a severe attack of arthritis which had produced much swelling and had involved the right elbow. This had been followed in three weeks by painful swelling of the right knee and right foot. Although the acute symptoms gradually had subsided, the involved joints had not returned to normal, as they had after previous similar attacks; instead, they remained moderately painful and swollen, and the range of motion had remained somewhat restricted.

Eight years previously, the patient had had a typical attack of renal colic and had passed a renal stone. Eighteen months before he came to the clinic, he had had a second attack of typical renal colic and had passed a renal calculus about the size of

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a grain of wheat. He had no recollection of the color of the calculi passed on either occasion.

Three weeks previously, his tongue had become sore and some redness had been observed on its margin.

When the patient was examined at the clinic, he had a pale pasty appearance and his hair was turning gray. His forearms and the dorsa of his hands were the color of tan leather. The skin was flabby and the subcutaneous tissues were atrophic. He had the characteristic appearance of a man who had lost considerable weight in a short time. His fingers showed a moderate degree of clubbing. The abdomen was protuberant and flatulent, and was doughy to palpation. Two tophi, the size of a millet seed, were observed on the rim of each ear. Material which was expressed from one of these tophi contained typical urate crystals. A tophus measuring approximately 2 cm. in diameter involved the left olecranon bursa. Smaller tophi were observed on the left elbow and on the dorsum of the right foot. His tongue was red

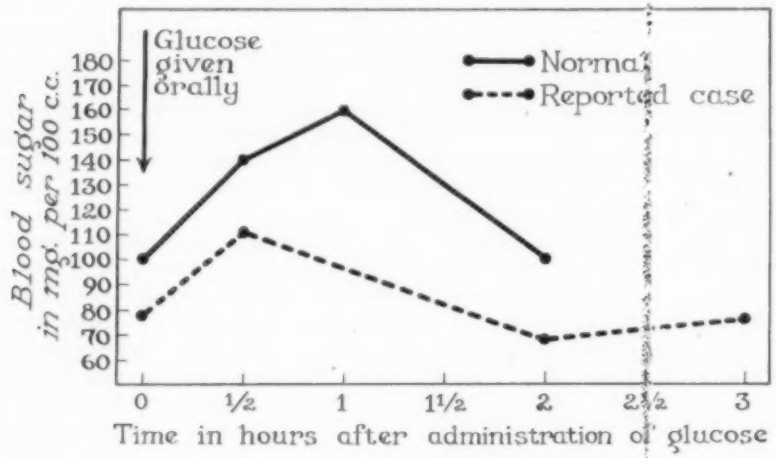

FIG. 1. Glucose tolerance curve in sprue compared with normal curve, modified from Todd and Sanford.[28]

and had smooth edges. The blood pressure was 120 mm. of mercury systolic and 82 mm. diastolic.

The specific gravity of the urine was 1.013 and the reaction was acid. Urinalysis disclosed albuminuria, grade 1 (on the basis of 1 to 4). The Kline flocculation test of the serum was negative. The concentration of hemoglobin was 12.5 gm. per 100 c.c. of blood. The erythrocyte count was 3,690,000 and the leukocyte count was 3,600. A differential white cell count revealed 56.5 per cent lymphocytes, 1.0 per cent monocytes, 30.0 per cent neutrophiles, 12.0 per cent eosinophiles and 0.5 per cent basophiles. Examination of a blood smear stained with Wright's stain revealed anisocytosis and macrocytosis with a relative leukopenia and eosinophilia. The shape of the blood corpuscles resembled that of the corpuscles of the peripheral blood seen in pernicious anemia. The values for the blood urea, serum calcium and serum phosphate, expressed in milligrams per 100 c.c., were 24, 8.2 and 2.9 respectively. The concentration of uric acid was 7.2 mg. per 100 c.c. of blood, as compared with an upper normal value of 4 mg. The concentration of serum protein was 5.7 gm. per 100 c.c. and the albumin globulin ratio was 2.3 to 1.0. The prothrombin time, determined by the method of Quick, was 22 seconds as compared with a normal value of

20 seconds. The value for the fasting blood sugar was 78 mg. per 100 c.c. and the response to the standard glucose tolerance test gave a flat curve (figure 1). This response has been recorded by previous writers on the subject [1, 2] and was noted by Snell,[3] in his report published in 1939.

The gastric secretory response was very much below normal and free hydrochloric acid was obtained only after stimulation by histamine, the highest concentration of free hydrochloric acid was 10 (according to the method of Töpfer) at the end of one

FIG. 2. Roentgenologic appearance of the small intestine; roentgenogram made one hour after ingestion of barium; the alterations in mucosal relief and pooling of barium are conspicuous.

hour. Roentgenographically, osteoporosis was noted in the right knee and the bones of the feet. The small intestine showed a characteristic picture of delayed motility, smoothing out of the contour of the lumen of the bowel with loss of the usual markings and a clumping of the barium in masses (figure 2). This picture in cases of idiopathic steatorrhea has been previously described by Snell and Camp.[4] Roentgenograms of the thorax, stomach and colon were normal. The kidneys were normal, as evidenced by intravenous urography. An excess of fat was noted in the stool but

a satisfactory quantitative estimation of this was not made. The basal metabolic rate was + 4 per cent. Neurologic examination was objectively negative except for some activity of the Chvostek sign. The diagnosis was tophaceous gout, gouty arthritis and nontropical sprue.

The patient was hospitalized because of a severe exacerbation of gouty arthritis which occurred in the course of his examination. This attack of arthritis proved unusually intractable and seriously hindered an adequate therapeutic approach to the sprue. The patient was confined to bed, the affected joints were supported on pillows, and moist hot packs were applied. For the acute episode, 1/100 grain (0.00065 gm.) of colchicine was administered orally at intervals of two hours until six doses had been administered. This resulted in prompt temporary subsidence of pain. Administration of cinchophen was then started. This drug was administered daily throughout the 37 days that the patient was in the hospital, except for two brief intervals of five days each. A total of 473 grains (31.5 gm.) of cinchophen was administered during this period. Sodium salicylate was administered in doses of 80 grains (5.3 gm.) daily on those days when cinchophen was not administered. Despite this full medicinal program, the symptoms of gout were not controlled effectively. At no time during our observation of this patient did he attain entire freedom from the pain of gouty arthritis; indeed, despite the fact that the concentration of uric acid in the blood was maintained within the normal range, he had several distinct exacerbations of swelling, redness and acute pain which involved his elbows, wrists, ankles and feet.

We had anticipated more than usual difficulty in treating this patient. We were faced not only with the necessity of relieving the pain caused by the gouty arthritis but we also were confronted with the urgent necessity of controlling the sprue. We felt that although control of the gout was needed and seemed immediately important to the patient because of the pain, the sprue, if uncontrolled, would undoubtedly be a serious menace in the future. A purine free diet has long been accepted by many physicians as an essential adjunct to the successful control of gout; on the other hand, it has been our experience that a high protein, low fat diet is helpful in the treatment of sprue. For these conflicting reasons, we considered it necessary to adjust the diet so that it would be as effective as possible in helping both of these conditions.

The specific effects of liver therapy in tropical sprue are well established.[5] Snell [3] said that a satisfactory response equal to that obtained in the treatment of tropical sprue by the intramuscular injection of liver extract was encountered in cases of nontropical sprue. He also noted that administration of liver extract in these cases caused a prompt reticulocyte response and rise in the erythrocyte count similar to that noted in pernicious anemia, a restoration to normal of the protein metabolism, an improvement in the utilization of fat and a restoration to a practically normal state of the roentgenologic appearance of the small intestine.

We anticipated that we might encounter difficulty in the use of liver extract in this case since it has been observed that the use of this substance in the treatment of pernicious anemia has provoked a first attack of gouty arthritis [6, 7] and the deposition of uric acid in the kidney.[8] A similar effect in other types of anemia has been noted by Fitz.[9] Since the use of liver extract in nontropical sprue results in an activation of erythropoiesis similar to that occurring in pernicious anemia, we expected that it would increase the concentration of uric acid and thus dispose to an exacerbation of the gouty arthritis. That active erythropoiesis results in an increased production of uric acid was shown by the work of Riddle [10] and Krafka.[11] As soon as the manifestations of gout were reasonably well controlled, however, we began the cautious administration of liver extract. We used a highly purified product and administered 1 c.c. daily intramuscularly. This particular preparation of liver extract is practically purine free and contains from 1 mg. to 1.6 mg. of purine per cubic centimeter. On the fourth day of the administration of the liver extract, a severe attack of gouty

arthritis occurred. No further attempt to use liver extract was made thereafter. As a substitute, ventriculin was administered in doses of 3 drams (12 gm.) daily. This seemed to be better tolerated, although gouty arthritis persisted in moderate degree.

Because vitamin deficiency in varying degree is associated with nontropical sprue, it is valuable to administer large doses of all of the vitamins. From the beginning of treatment, the patient daily was given 10 mg. of thiamine chloride, 5 gm. of brewers' yeast, and 3 capsules containing high amounts of vitamins A and D. In addition to this medication, 2 gm. of ferrous sulfate and 3 gm. of calcium gluconate were administered daily.

Throughout the patient's stay in the hospital, the manifestations of nontropical sprue were not well controlled. This we felt possibly was due to the fact that treatment of the sprue was always seriously curtailed by the treatment needed for the complicating gouty arthritis. The patient continued to have from three to four bulky stools daily. All of these stools had a high fat content. During the last week of his stay under our observation, there was a gradual amelioration of the arthritis and some improvement in the character of the stools.

The patient was instructed in a modified low purine diet and was advised to take 539 gm. of carbohydrate, 143 gm. of protein and 43 gm. of fat daily. He was advised to continue the use of calcium and iron and the vitamin concentrates. For his gout, he was advised to take 22.5 grains (1.5 gm.) of cinchophen three days each week and on the following three days to take daily doses of 60 grains (4 gm.) of sodium salicylate and 150 grains (10 gm.) of glycine.

We have learned that during the three year interval since this patient was under our care he has had repeated recurrences of gouty arthritis of a mild character. These attacks are readily controlled by an intensification of the therapy outlined for the gout. The nontropical sprue has been poorly controlled and he has continued to have two or three loose bulky stools daily. His tolerance to an adequate regimen for the control of the sprue has not improved, and at the time this paper was written it would appear that the outlook for complete control of his two conditions is not good. Even though his improvement has not been as satisfactory as one could hope for, it has been satisfactory enough to justify a continuance of the rather full therapeutic program outlined.

Comment

This case emphasizes a fact well recognized by students of the sprue syndrome, namely, that the condition can affect a patient who has never lived outside the temperate zone. It is worthy of emphasis that in this case the symptoms of an abnormal bowel habit were evident throughout the greater share of the patient's life. The occurrence of voluminous and frequent stools was of such long standing that he considered it normal for him. Undoubtedly, the sprue antedated the onset of the clinical manifestations of gout, but when the latter became manifest the symptoms of the sprue coincidentally became much more aggravated.

The presence of gout in this case coincident with the macrocytic anemia of nontropical sprue further extends a considerable body of data linking the metabolic fault of gout to many hematologic disorders associated with disturbances in the quantitative metabolism of uric acid.

In cases in which gout is uncomplicated by any independent disorder of the blood or blood forming organs, one generally finds no deficiency of hemoglobin or of the number of circulating erythrocytes. For this reason, one may expect to find some additional complicating disease in a case of gout in which anemia is present. Generally, this complication is found to be deficient renal function, for

anemia paralleling the severity of renal insufficiency is almost constantly present in cases of gouty nephritis. Duckworth [12] was impressed with these observations at a time when determination of the number of circulating elements in the blood was attempted only occasionally. In 1890, he pointed out that "Corpuscular richness is not affected in gout, the red globules being in full number. The leukocytes are not increased." In 1940 Kinnell and Haden [13] reported that erythrocyte counts less than 4,000,000 per cubic millimeter were observed in only three of 62 cases of gout. Of this series of patients, half were found to have erythrocyte counts of 4,800,000 or more, and hemoglobin values of 90 per cent or more.

In this relative constancy of a normal condition of the blood, gouty patients differ strikingly from patients with rheumatoid arthritis and from patients with active rheumatic fever. In both of these latter conditions the incidence of significant grades of anemia is relatively high.

In cases of gout, the number of circulating leukocytes is generally normal during the periods when the patients are free of articular symptoms; however, one frequently encounters leukocytosis with counts ranging as high as 20,000 leukocytes per cubic millimeter during the acute attacks of gouty arthritis.

Numerous authors [14, 15] have reported the coincidence of gout and various leukemic states. Lambie [16] reviewed the bibliography of this subject in detail. This association of diseases has given rise to considerable speculation regarding the possible mechanism involved. It is known that patients with leukemia frequently excrete large quantities of uric acid and have an associated hyperuricemia. Presumably, this hyperuricemia and the accompanying urate diuresis are related to the heightened hematopoietic function current in cases of leukemia. However, only occasional susceptible individuals experience gout during the course of leukemia. The metabolic link responsible for this occasional association has not yet been determined with certainty.

The occasional association of gout and primary or pernicious anemia was reported by Spence [17] one year after the introduction of liver as a successful form of treatment for pernicious anemia. He reported that he had observed harmful results from too vigorous administration of liver after control of the pernicious anemia. Three of his patients had taken a pound of liver daily for three months, after which the blood had returned to normal. In two of the cases acute attacks of gouty arthritis developed during this treatment. Davidson and Gulland [18] drew attention to the reported coexistence of the two diseases, and Sears [6] reported the occurrence of acute attacks of gout after the use of liver therapy for pernicious anemia. We also have observed such cases. Hench [19] repeatedly has warned of the danger of provoking acute attacks of gouty arthritis by administering liver to gouty patients.

In pernicious anemia, as in leukemia, curious anomalies of uric acid metabolism have been detected. The improvement phases which result from liver therapy are associated with an elevation of the concentration of uric acid in the blood and in a considerable diuresis of uric acid, presumably a result of the breaking down of nuclei extruded from the normoblasts,[7, 10, 11] a process which is speeded up greatly in the recovery phase of this condition. However, here, too, the metabolic link with gout is undetermined. In the case we are reporting, an attack of gouty arthritis occurred after administration of liver extract which was essentially free of purine. Whether or not this patient had a dis-

turbance of purine metabolism analogous to that occasionally encountered in true primary macrocytic anemia after liver therapy, we were not able to determine.

A further striking relationship of gout to the diseases of the blood and blood forming organs is seen in the occasional association of gout and erythremia. In this latter disease the hyperuricemia which is occasionally present has been attributed by Isaacs [20] to the increased rate of production of erythrocytes from normoblasts with the accompanying extrusion and destruction of a large number of nuclei from these cells.

By means of experiments on dogs, Krafka [11] found that the rate of excretion of uric acid by exsanguinated animals was twice that by normal animals. In the case of human beings, hemorrhage of considerable magnitude may provoke an attack of gouty arthritis. An early report of this association was attributed to Syndenham,[21] who is said to have noted the relationship of attacks of gout to venesection. This observation has more recently been made by Ewertson and Meulengracht,[22] who noted that gouty arthritis occurred after large hemorrhages into the gastrointestinal canal. Gouty arthritis has been known to develop in cases of congenital hemolytic icterus.[23, 24] Lambie [16] observed that other poorly classified types of anemia may be associated with gout.

These data clearly must be explainable in relation to the case of macrocytic anemia, nontropical sprue and gout which we have reported. Our observations point seemingly to some common but still unknown factor which causes the association of gout, gouty arthritis and diseases of the blood. Careful clinicians will try to spare the unfortunate gouty patient the pain of unnecessarily provoked attacks by avoiding the use of liver extracts whenever possible. If this cannot be done, one will have to move carefully between the attendant dangers of administering the drug and of treating the hematologic anomaly as required.

This case presents a further important consideration when one attempts to explain the apparent detrimental effect on the clinical course of the gout motivated by the treatment of the nontropical sprue. We refer to the effect of the liver extract in restoring to normal the absorptive power of the small intestine. As was noted, the small intestine in this case showed the abnormal changes that are characteristically seen in nontropical sprue. These changes included delayed motility, smoothing out of the contour of the bowel, and the clumping of the barium in masses. There is evidence to show that such a small intestine lacks a normal absorptive capacity. Fairley [25] said that decreased absorption from the intestine in such cases explained the abnormal response to the glucose tolerance test. The characteristic abnormality of response of the blood sugar after the ingestion of dextrose is manifested by a flat blood sugar curve (figure 1). Moreover, Barker and Rhoads [26] pointed out that the concentration of lipids in the blood does not rise after the ingestion of a fat meal in cases of sprue. They said that the excessive amount of fat in the stool is a manifestation of the inability of the intestinal mucosa to perform its absorptive function normally. They inferred that the diarrhea noted in such cases is not the cause of the lack of normal absorption of fat but the result of it. They suggested that liver extract, when administered in such cases, acts on the intestinal mucosa and improves its ability to absorb fat. They noted that, coincident with the improvement of the patient under treatment by liver extract, the concentration of blood lipids increased, the fat content in the stool diminished and the diarrhea lessened.

Not only is the absorption of dextrose and fat affected by treatment but the improvement in absorption of protein is equally important.

Erf and Rhoads [27] showed by means of a glycine tolerance test that amino acids are poorly absorbed in cases of untreated sprue. They found that liver extract, given until symptomatic improvement occurred, would correct this abnormality of utilization of the amino acids. On the basis of this evidence, it is reasonable to infer that, in cases of sprue in which liver extract is being administered, the improved absorptive ability of the small intestine might permit the entrance into the blood stream of a high concentration of purine substances, since the diet given for sprue is normally high in purines. That such a state of affairs might precipitate gouty arthritis in a case in which gouty diathesis or actual gout coexists seems highly probable.

Summary

The case which we have reported illustrates an unusual association of nontropical sprue and tophaceous gout with severe gouty arthritis. The conflicting therapeutic measures indicated in the control of these two metabolic diseases made adequate control of the two conditions impossible. We are unable to draw any conclusions as to a possible etiologic effect which either condition had on the other.

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GENERAL SANARELLI-SHWARTZMAN PHENOMENON WITH FATAL OUTCOME FOLLOWING TYPHOID VACCINE THERAPY *

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Instances of sudden death after intravenous typhoid vaccine therapy have appeared sporadically in the literature (Hench,[1] Cecil,[2] Ziskind and Schattenberg,[3] Lewis,[4] Russel [5]). No uniform opinion exists concerning the mechanisms responsible for death. A number of possibilities have been considered by various authors: (1) disturbances of the neurovascular system (acute vasomotor collapse) (Cecil [2]), hyperpyrexia (Russel [5]), (2) vascular changes (disturbances in the capillary permeability), chemical changes leading to acute thrombosis (Hench [1]), (3) stimulation of inflammatory foci of infectious origin (Hench [1]), (4) anaphylactic shock (Ziskind and Schattenberg,[3] Russel [5]).

On the basis of the case reported herein and the experimental work of

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Sanarelli [6] and Shwartzman,[7] another mechanism must be added to this list, namely, that of the general Sanarelli-Shwartzman phenomenon.

There are two forms of hemorrhagic phenomena associated with the name of Gregory Shwartzman—the local Shwartzman phenomenon and the general Sanarelli-Shwartzman phenomenon. Since there is some confusion about these two types, a brief discussion may be of some value. The local phenomenon can be produced in experimental animals by preparing a skin site with bacteria-free filtrate as typhoid bacillus culture and injecting a filtrate of the same or a different bacterial culture intravenously 24 hours later. For the preparatory as well as for the provocative factor many other agents may be used. A severe hemorrhagic-necrotic reaction, confined to the prepared skin site, will appear within a few hours. A detailed discussion may be found in a recent paper by the authors.[8]

In order to call forth the general reaction, it is necessary that preparatory and provocative bacterial agents, which in themselves do not produce reactions, be injected intravenously at a 24 hour interval. This results in a severe reaction with cutaneous and visceral hemorrhages. The histologic changes in experimental animals show severe extravasations of blood, chiefly fibrin, in the veins of the liver, spleen, pancreas and lungs, and arterial necrosis in the kidneys, adrenals and bone marrow. In addition to fibrin thrombi in the glomerular capillaries of the kidney, there is extensive necrosis of the tubules and glomeruli. Concurrent with the vascular lesions, there is observed focal necrosis in the malpighian corpuscles of the spleen, in the lobules of the liver and in the heart muscle.

Since this particular experimental work was first performed and described by Sanarelli,[6] the generalized hemorrhagic reaction is properly called the Sanarelli-Shwartzman phenomenon.

Finally, both the local and general phenomena may coexist in the same individual. Thus, the authors [8] described a case of severe hemorrhagic-necrotic reaction to tuberculin P. P. D. in a tuberculous patient, followed by death in four weeks. The presence of free blood both in the peritoneal cavity and in the lumen of the intestines, and diffuse hemorrhages in the wall of the gastrointestinal tract at autopsy strongly suggested the possibility that the general form was present as well. The following is the first reported case, a typical general Sanarelli-Shwartzman phenomenon in a human being, and merits description for that reason.

Case Report

The patient, a 40 year old housewife, was admitted to the Jewish Hospital on January 14, 1941 to the service of Dr. E. Heller, with the complaint of backache extending down the back of the left thigh and calf to the ankle. It had been present for seven years, and had been increasing in severity for some time before admission. For five years the patient had had pain and stiffness in both knees and the fingers of both hands.

The past medical history was negative, except for four miscarriages. The family history revealed that her father, a sister and a son had died of pulmonary tuberculosis.

Physical Examination. The patient was markedly obese, weighing 157 pounds. She was comfortable only in the supine position. The temperature, pulse and respiratory rates were normal. The blood pressure was 108 mm. Hg systolic and 64 mm.

diastolic. There were tenderness over the midthoracic and lumbar vertebrae and limitation of motion of the spine upon flexion. Crepitus and pain on motion of the left knee were noted. Laseque's sign was positive. The interphalangeal joints were negative. Gynecologic investigation disclosed a chronic endocervicitis and parametritis.

Studies. The urinalysis, blood count and chemical determinations, including urea, uric acid, calcium, phosphorus and cholesterol were within normal limits. Serologic tests for syphilis were negative. Sedimentation rate was 11 mm. in one hour. Roentgenogram showed a markedly narrowed lumbosacral disc.

Clinical Course. A diagnosis of infectious arthritis was made. Fourteen days after admission the patient was given triple typhoid vaccine, 10 million organisms intramuscularly followed in half an hour by 50 million intravenously. There was no reaction. The next day the same technic was employed using 10 million organisms by the intramuscular route and 75 million intravenously. There was a sharp reaction; the temperature rose to 101° F., returning to normal in eight hours. The following day the same doses were repeated and although a severe chill ensued, the temperature rose only gradually to 99.6° F. in a period of two hours, after which it dropped precipitously to 96.4° F. The pulse rate mounted to 140 per minute, the blood pressure fell to 50 mm. Hg systolic and 20 mm. diastolic, and signs of shock appeared. Despite vigorous shock therapy, including adrenalin, coramine and oxygen, the patient died six and one-half hours after the injection.

An *autopsy* was performed by Drs. D. Fishback and D. Woldow 16 hours after death. There were numerous purpuric lesions on the skin. Petechiae were present in the parietal pericardium, endocardium, and on the surface of the liver. The kidneys also were studded with small, discrete hemorrhages of linear character. The musculature of the body was unusually dark and intensely congested, dripping blood on sectioning. Both lungs were extremely congested and edematous, showing localized hemorrhagic zones in the subpleural regions. The liver was unusually soft, pale and pliable. The heart was markedly dilated, the myocardium poor in tone, and showed myocardial degeneration with fatty infiltration of the myocardium. Microscopic study revealed acute tubular necrosis (nephrosis) of the kidneys, and medullary necrosis and hemorrhage of the adrenals; acute hepatic necrosis, acute capillo-venous congestion of the lungs.

Summary. A 40 year old woman with infectious arthritis died with the clinical picture of circulatory collapse a few hours after the third intravenous injection of typhoid vaccine, preceded each time by an intramuscular injection. At autopsy there were widespread cutaneous and visceral petechial hemorrhages, lack of coagulation of the blood, intense congestion of the lungs and muscles associated with renal, hepatic and adrenal necrosis.

Comment

The striking similarities between the autopsy findings in this case and those in experimental animals in which the general Sanarelli-Shwartzman phenomenon has been induced, provide the justification for explaining the death following repeated typhoid vaccine injections on this basis. The widespread petechiae in the internal organs, the purpura of the skin, the acute necrosis in the tubules of the kidneys, in the parenchyma of the liver and in the medulla of the adrenals, all correspond rather closely to the experimental observations. Since there is nothing else in the history, clinical course or treatment to account for these hemorrhages and acute necrosis other than the typhoid injections, the latter must be held responsible for the unfortunate occurrence.

The question then arises as to why these injections, given without harm so many thousands of times, should in this case call forth this unusual lethal reaction. Although we are unable to prove it, we would like to present the following hypothesis as an explanation of such instances of sudden death which show hemorrhages and necroses of internal organs both clinically and at autopsy.

The induction of the general Sanarelli-Shwartzman phenomenon in experimental animals depends on two factors, a preparatory and a provocative bacterial toxin, both administered intravenously. In the human being, however, a somewhat different mechanism has to be assumed, since bacterial toxins are never injected intravenously. Nevertheless, it occurs quite frequently that bacterial toxin is thrown into the circulation from a focus of infection. This may be followed by a hemorrhagic and necrotizing lesion in an individual organ, producing, for instance, a hemorrhagic-necrotic appendicitis, pancreatitis, acute glomerulonephritis or possibly hemorrhagic gastritis (Albus [9]). If this happens and no other pathogenetic mechanism can be demonstrated, a local Shwartzman phenomenon may properly explain these severe, local hemorrhagic-necrotic processes.

On the other hand, there are no instances known, in which bacterial toxins entering the circulation from a focus of infection have called forth a disease picture corresponding to that of the general Sanarelli-Shwartzman phenomenon in experimental animals. It is necessary, therefore, to postulate such a combination of factors as to be analogous to the experimental conditions. In this connection, attention should be called to the fact that each intravenous injection of typhoid vaccine was preceded by an intramuscular injection one half hour before, and this treatment was on three consecutive days. Assuming that a patient with infectious arthritis of seven years' duration may have a focus of infection, it is easy to conceive that the repeated stimuli would greatly increase the specific antibodies (anamnestic or metaspecific reaction [10]). The frequently repeated injections may have activated the focus of infection (the patient had evidence of a chronic pelvic infection) and rather suddenly liberated bacterial toxin into the circulation. As a result the following factors came into play: the preparatory principle consisting of an antigen-antibody reaction with the typhoid vaccine as a heteroantigen [9] reacting with the specific antibody; and secondly the provocative principle represented by the circulating bacterial toxin originating from the activated focus of infection. The combined interaction of all of these factors, probably rarely encountered in human beings, may explain the occurrence of the general Sanarelli-Shwartzman phenomenon in man.

It may be asked, whether the product of an antigen-antibody reaction can replace bacterial toxin as the preparatory principle. Since this was found to be satisfactory in the local preparation of a skin site for the Shwartzman phenomenon, it would seem reasonable that the same holds good for the general phenomenon, because the difference between them depends on whether a local site or the whole organism (by the intravenous route) is "prepared" (Alechinsky [11]).

Can this explanation be upheld in view of the fact that a large number of typhoid vaccine injections, in a divided dose technic, were given even for 10 consecutive days without untoward reactions (Weinberg and Goldstein [12])?

The answer may lie in the different immunologic state of the patients studied by these authors; they were neurosyphilitics who, as is well known, have a very low response to any immunotherapy. This implies that no antigen-antibody reaction with the typhoid vaccine as a heteroantigen will ensue.

Finally, we would like to call attention to some of the autopsies and clinical observations which seem to be consistent with our belief that the mechanisms underlying the Sanarelli-Shwartzman phenomenon are sometimes the cause of severe or fatal reactions, following typhoid vaccine therapy. Thus, the autopsy of Ziskind and Schattenberg's case [3] of arthritis showed petechiae in the pleura and epicardium and extreme congestion of the liver. They explained these on the basis of an anaphylactic shock of the "dog type." Opinion is divided, however, as to whether anaphylactic shock of the dog type may occur in human beings, because there is no proof that the liver can be the shock structure in man. The striking similarities between the autopsy findings in their case and ours leads us to explain both on the same basis. Furthermore, Hench,[1] Russel,[5] and Lewis [4] found clinical and postmortem evidences of acute nephritis following typhoid vaccine therapy, which may indicate the presence of a local Shwartzman phenomenon in the kidneys.

Summary

An instance of sudden death following intravenous typhoid vaccine therapy in a patient with arthritis is reported.

The autopsy revealed widespread cutaneous and visceral petechiae, intense congestion of the lungs and intestines and renal, hepatic and adrenal necrosis. These findings correspond to those of the general Sanarelli-Shwartzman phenomenon in experimental animals.

Clinical facts representing the preparatory and provocative principles of the generalized Sanarelli-Shwartzman phenomenon in this case are presented.

For these reasons the death in this patient and in a second one reported by Ziskind and Schattenberg may be explained on the basis of the generalized Sanarelli-Shwartzman phenomenon.

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UNCOMPLICATED, SOLITARY, SEROUS RENAL CYST WITH HYPERTENSION RELIEVED BY NEPHROCYSTECTOMY *

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THE investigative impetus, from the brilliant researches by Goldblatt and his associates and others [1, 2, 3] on the establishment of elevated blood pressure by interference with the renal blood supply of animals and by various operative procedures on the kidneys and ureters of animals, has produced, in the past two years, a large clinical literature on the renal basis for hypertension.[4, 5, 6, 24]

Experimentally, removal of the diseased kidney has abolished the hypertension.[2, 7] This has been observed in man after nephrectomy.[4, 5] That the fall in blood pressure in long standing renal disease may not reach normal, after nephrectomy has been performed, has also been demonstrated.[6]

We feel that the following case is noteworthy because it demonstrates the production of hypertension from renal atrophy with interstitial fibrosis due to pressure from the growing cyst without antecedent infection. It is also worthy of recognition because the patient was normotensive three and one-half years after nephrocystectomy.

CASE REPORT

H. H., aged 40, male, Negro, was admitted to the surgical service of Dr. John O. Bower at the Philadelphia General Hospital March 12, 1939 complaining of "piles for eight months" and a "swollen stomach for one and one-half years."

One and a half years before admission, he had noticed progressive abdominal enlargement. This had continued for six months and remained stationary thereafter. Pain had never been present. Constipation associated with bleeding prolapsed hemorrhoids had been present for eight months prior to admission. He had been unable to reduce the prolapsed hemorrhoids for three days before entering the hospital. There was no history of abdominal trauma.

He was aware of some weight gain but not certain of the amount. Dyspnea on exertion had occurred shortly prior to hospitalization. He voided clear urine eight to 10 times daily and five to six times at night.

A right inguinal herniorrhaphy had been performed 13 years before. The past history was otherwise irrelevant. He had been married for 17 years; his wife had borne one living child and a stillborn. He indulged in alcohol occasionally. Family history was not significant.

On admission his temperature was 99.2° F., pulse 78, and respirations 22. Head

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From the Surgical Service of Dr. John O. Bower, Philadelphia General Hospital.

and neck were normal. There was some flaring of the lower costal cage and widening of the subcostal angle. The lungs were normal. The apex beat was in the fifth interspace 1 cm. within the midclavicular line. Heart sounds were loud and snappy. The initial systolic sound was rough. $A_2 > P_2$. Blood pressure in the left arm was 170 mm. Hg systolic and 120 mm. diastolic and in the right arm, 150 mm. Hg systolic and 110 mm. diastolic. Radial pulses were equal and synchronous.

The abdomen was distended to the size of a term pregnancy with an irregular contour owing to displacement of the bowel by a large cystic mass through which a fluid wave was obtained. The mass was the size of a basket ball and occupied principally the left abdomen, extending about one-third over the midline. About two-thirds was above the umbilicus. No bruit or thrill was elicited. Stationary flank dullness was obtained. The spleen and liver could not be palpated. A right inguinal hernia scar was present. Large, prolapsed hemorrhoids were evident. The admission impression was pancreatic or mesenteric cyst, hypertensive cardiovascular disease, possible syphilitic aortitis, and prolapsed hemorrhoids.

Dr. Bower thought the cyst sprang from the tail of the pancreas. Renal cyst was considered as a second possibility, but it was thought the increased blood pressure was on the basis of increased extrinsic pressure on the aorta. The urinary frequency was thought to be caused by pressure on the bladder.

Hemoglobin was 12 grams, red cell count 4.56, and the white cell count normal. Three repeated urine specimens were normal. Blood chemistry and serology were negative. Gastric analysis was normal. Electrocardiography was negative. Orthodiagraphy only demonstrated slight left axis deviation.

Roentgenographic report by Dr. J. Fetter stated: "Fluoroscopically, the esophagus and swallowing function are normal. Stomach is displaced upward, somewhat to the left, and greater curvature is concave due to pressure by a smooth, extrinsic tumor mass, which appears as a circular area of density, occupying the greater portion of the abdomen. There is considerable widening of the duodenal loop and the small bowel is displaced anteriorly and to the right. The tumor mass is encircled by the colon which passes above and to either side. There is no evidence of intrinsic disease of the stomach or duodenum. The appearance is most likely due to a large cyst of the pancreas."

His preoperative blood pressure on March 20, 1939 was 160 mm. Hg systolic and 100 mm. diastolic.

Operative note (March 20, 1939, Dr. John O. Bower). Under open drop ether anesthesia, an upper left rectus incision was made. The peritoneal cavity contained a large cystic mass, covered by mesothelial tissue, extending down into the pelvis. The cyst was mobilized and found to be 28 centimeters in diameter. It seemed to arise from the posterior parietes and had no connection with the pancreas or the mesentery. Four litres of clear serous fluid with a uriniferous odor were then aspirated. The cyst was then picked up, the aspiration puncture enlarged, and several small openings on its inner surface found. The ureter was then mobilized and a catheter introduced into it from within the cyst. Deep along the posterior surface of the cyst were found some atrophic islands of parenchymatous renal tissue. The ureter was then transected at the bladder and the cyst removed completely. A Penrose drain was inserted in the retroperitoneal space and brought out through a stab wound in the loin. The wound was closed in layers. Convalescence was uneventful.

Blood pressure readings were: (3–22) 120/70; (3–23) 120/80; (3–24) 122/75; (3–25) 122/78; (4–5) 120/80. He was discharged on April 5, 1939.

Pathologic diagnoses: Specimen consisted of a large, collapsed cyst with a smooth wall. In a portion was contained the remains of a kidney. Microscopic diagnosis by Dr. H. M. Dixon noted that low power ($\times 40$) magnification of a section through the edge of the cyst, including a narrow rim of atrophic renal paren-

chyma, shows interstitial fibrosis and chronic inflammation. The epithelial lining is shown along one edge and demonstrates slightly columnar epithelium (figure 1).

The patient was watched in the follow-up clinic at intervals of three months up to August 1942. During this time his systolic pressure varied between 118 and 130 mm. Hg and his diastolic ranged from 80 to 86 mm. Hg. An intravenous pyelogram on August 16, 1940 revealed: "the right kidney is well outlined and there is evidence

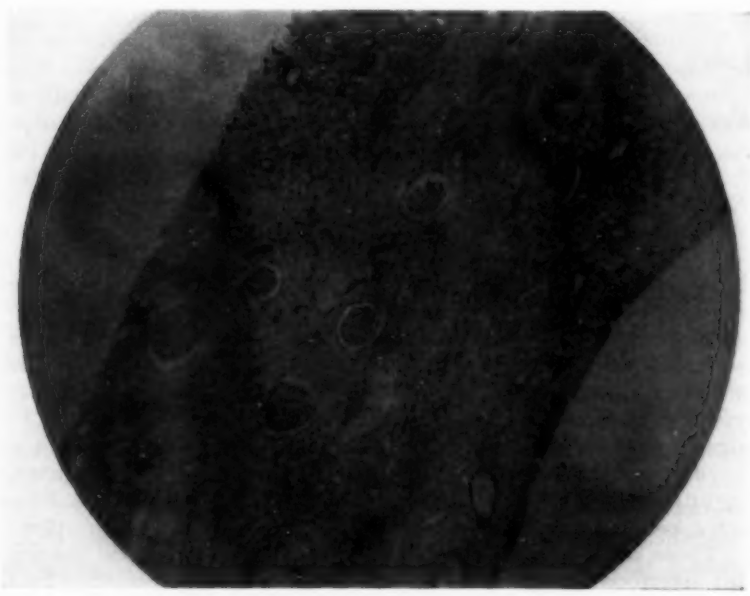

FIG. 1. Low power (× 40) magnification of a section through the edge of the cyst, including a narrow rim of atrophic renal parenchyma. This demonstrates interstitial fibrosis and chronic inflammation. The epithelial lining is shown along one edge and presents slightly flattened columnar epithelium.

of dilation of the pelvis and particularly the calyces. The bladder is normal. No calculi are present." His urinary frequency subsided immediately after leaving the hospital and he now micturates five to six times during the day and once at night.

DISCUSSION

Incidence. Solitary cysts of the kidney are uncommon. Up to 1924, 95 cases were recorded.[9] McKim and Smith,[10] and Laquière [11] collected 120 cases. Hepler [12] reviewed 212 cases and added seven cases of serous cysts of his own, in 1930. The variability of occurrence has been pointed out by Fish.[13] He stated that none was found in 12,500 cases up to 1926 in the Brady Institute of the Johns Hopkins Hospital, whereas he was able to collect 32 in 11,879 urologic cases, 4,011 of which were renal, at the Presbyterian Hospital in New York City. However, we had not been able to discover any case with hypertension wherein the blood pressure fell to normal limits following nephrocystectomy during our first two years of follow-up study. In February 1942, Farrell and Young [15] reported such a case with a 10 month follow-up study. Our case antedates theirs. Robinson and Wilder [14] observed that more than 300 cases of solitary

renal cysts had been recorded in 1938. Since that time, numerous reports have been made of new cases. Many of them are in the foreign literature. Considering the reduplicative processes of case collecting, we have estimated some 400 recorded cases of this condition.

Etiology and Pathology. Herman [16] quotes Beer [17] that "the sum of the evidence offered seems to support the view that simple serous cysts originate from the lymphatic spaces situated between the layers of the true capsule, possibly through a traumatic or inflammatory agency." Robinson and Wilder [14] state that the cysts usually arise in the cortex near the surface and then thin fibrous walls are formed by the compressed adjacent parenchyma. Enucleation is not possible because the parenchyma of the kidney forms its walls and resection or nephrectomy is therefore necessary. Age incidence is 30 to 60 years, the average being 42.7 years. Mixter [18] performed nephrocystectomy on a girl aged 13 months and observed that only six cases had been recorded in children under 10 years of age. Since then some have been reported but many of the writers attest to its rarity among pediatric autopsy and clinical material. This fact suggests the view that solitary cysts are acquired. The absence of a capsule histologically supports this. Hepler [12] has produced cysts in rabbits by obstructing the arterial supply and tubular drainage of the same renal segment.

On the other hand, the congenital theory is championed by Kampmeier,[19] Reinhoff,[20] and Latteri.[21]

In Fish's [13] series the largest contained 10 liters and the smallest 350 c.c. of fluid.

Diagnosis. Females are afflicted more than males (66.6 per cent). Only large cysts are clinically demonstrable. Symptoms lasting from one day to 20 years have been noted. They may be short but are apt then to be associated with mild urinary tract difficulty. Hematuria is present in less than 10 per cent of cases. Pain may occur from pressure on surrounding structures. Renal colic is rare. Dragging or aching sensations, jaundice, and cardiorespiratory difficulty may be caused by pressure in cysts of the upper pole.[22] The pyelogram may be normal if there is no pressure deformity. The plain roentgenographic film often shows the cyst which Hinman [23] points out may be calcified rarely. The total phenolphthalein test may be normal and unilateral reduction may not be present. However, renal failure may be marked if the condition is bilateral. Usually, the mass is palpable and ptosed. Under differential diagnosis, one should consider hydronephrosis, hypernephroma,[24] polycystic kidney, hydatid cyst, dermoid cyst, cysts of the spleen, liver, pancreas, mesentery, Wolffian body, urachus, and ovary, extrarenal tumor, retroperitoneal sarcoma, and hydrops of the gall-bladder.

Treatment. Resection of the cyst with its surrounding parenchymal renal tissue without removal of the kidney is ideal. If the cyst is large or the kidney markedly atrophic, nephrectomy is indicated. Aspiration and the instillation of sclerosing solutions have been advocated by Fish [13] and others.

Summary

We have presented a case of solitary serous renal cyst with hypertension. After nephrocystectomy, the blood pressure returned to normal and has remained so for three and one-half years. We believe this to be the first case of

its kind observed and the second recorded. A review of the literature of solitary renal cysts is appended.

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EDITORIAL

AN EXTRAORDINARY RECORD

THE accomplishments of the Medical Corps of the Army and Navy in protecting the health of the men in the Armed Forces have justly been a source of pride and satisfaction to all members of our profession. Probably few of us, however, have realized fully how remarkable these achievements have been. Those members of the College who were able to attend the Annual Meeting in Chicago, March 31, had the opportunity to learn something about this record from senior medical officers who have taken an important part in directing these activities. Colonel Holbrook discussed some of the measures employed in handling battle casualties, and Brigadier General Hugh J. Morgan recounted some of the feats of our internists in the treatment of disease. We are fortunate in being able to publish Brigadier General Morgan's address in this number of the ANNALS OF INTERNAL MEDICINE, and we commend it to the careful attention of our readers.

The success attending the treatment of surgical conditions has been relatively better appreciated than that of our internists. It is nevertheless heartening to learn that the mortality among the wounded has been reduced to 40 per cent of that in the first World War, and that 97 per cent of the wounded admitted to Army hospitals recover. Many factors have contributed to this, but none more than the excellent training, skill, and devotion to duty of the medical officers. Better emergency treatment at the front, care to minimize shock by evacuating the wounded by air to the immediate vicinity of the hospitals, the timely use of plasma, improvements in surgical technic and control of infections by chemotherapy have all played a part in this success.

The results obtained by our internists in the treatment of ordinary diseases, however, have been even more impressive. General Morgan has given a striking example of this by comparing the fatality rates of four important infectious diseases during this war with those during the first World War. Thus the fatality rates from tuberculosis and from meningitis have been reduced to about one-ninth, that of dysentery to one-thirtieth, and that of pneumonia to one-fortieth of the rate in World War I.

Here, too, we must give credit first of all to the superior training and skill of our medical officers, a large majority of them Reserve Officers, who have been capable of utilizing in full measure the ample facilities provided for reaching an accurate diagnosis, as well as applying the newest and most effective methods of treatment. The American College of Physicians may take pride in the active part it has taken in improving the education and training of these men.

Most spectacular of all, perhaps, is the reduction in the total annual death rate in the Army from disease (excluding injuries). From an average

annual death rate of 15.6 per 10,000 men in World War I, it has been reduced to 0.6. This is a reduction in death rate from diseases other than injuries of more than 95 per cent. Here preventive medicine as well as curative medicine has played its part.

Less than 50 years ago, deaths from disease in the Army during war far outnumbered deaths from battle casualties. The spectre of typhoid fever, typhus and other infections was justifiably more terrifying than the enemies' bullets. One needs but recall the ravages of typhoid and dysentery during the Spanish-American War. Today most illness in the Army is brief and results in recovery. Preventive medicine has eliminated many of the most dangerous infections. Aside from battle injuries, the Army, instead of being a grave menace, has become one of the most healthful spots in which a young man may find himself. If he should be unfortunate enough to become ill, the skillful medical care and ample hospital facilities available, even near the fighting fronts, make his chance of recovery as good if not better than it would be in any other place in the world. The friends and families of our fighting men would get great comfort from a full realization of these facts, if they were generally known.

REVIEWS

Medical Physics. First Ed. By Otto Glasser (Editor in Chief), Ph.D., Head, Department of Biophysics, Cleveland Clinic Foundation; Professor of Biophysics, Frank E. Bunts Educational Institute; Consulting Biophysicist, University Hospitals of Cleveland, Cleveland, Ohio. *Associate editors:* Normand L. Hoerr, M.D., Ph.D., Otto Rahn, Ph.D., Charles P. Winsor, Ph.D., George W. Binkley, M.D., Eric Ponder, M.D., D.Sc., Russel Haden, M.D., W. James Gardner, M.D., Robley D. Evans, Ph.D., Albert D. Ruedemann, M.D., W. B. Rayton, D.Sc., James A. Dickson, M.D., Paul M. Moore, Jr., M.D., Harry Goldblatt, M.D., C.M., Norman C. Wetzel, M.D., Leo C. Massopust, Francis M. Whitacre, Ph.D., Walter J. Zeiter, M.D., John G. Albright, Ph.D., Harold D. Green, M.D., Harry Hauser, M.D., Frederick R. Mautz, M.D., Charles C. Higgins, M.D., and 250 contributors (including the associate editors). 1744 pages; 19 × 27 cm. The Year Book Publishers, Inc., Chicago, Ill. 1944. Price, $18.00.

Medical Physics is an unique attempt to correlate the principles of physics and their application to medicine, both experimental and clinical. According to the editor, the volume was compiled to serve a threefold purpose: "a combination of an encyclopedia, sufficiently comprehensive to serve all those whose occupations involve any aspect of medical physics; a textbook, adequately detailed in exposition to serve students; and a working instrument in which may be found data necessary for actual application of the principles of physics to medicine."

The book consists of a series of reviews written by 250 authorities in chemistry, physics, engineering, biology, and various medical specialties and covering theory, apparatus and methods, and applications of physics to medicine. The papers are arranged in alphabetical order without regard for continuity of subject matter, making it somewhat difficult to correlate the material. This difficulty is compensated for to some degree by a classification of the articles in a special table of contents under 23 general topics: anatomy, bacteriology, biometrics, biophysics, dermatology, hematology, medicine, neurology, nuclear physics, ophthalmology, optics, orthopedics, otolaryngology, pathology, pediatrics, photography, physical chemistry, physical therapy, physics (instruments and methods), physiology, radiology, surgery, and urology. There is a certain amount of overlapping in the papers written by different men and some topics are presented in a more comprehensive fashion than others. Frequent digressions into related fields, particularly biochemistry, are inevitable. This often adds to the value of the book.

The sections on theory, apparatus and methods are quite complete. Explanatory diagrams are frequently included and the underlying mathematical derivations are presented where they are required. Several tables of physical constants are included.

The bibliographies are extensive. They are not uniform, however, and some are difficult to follow because the references given in the text are in numerical sequence and the bibliography is arranged in alphabetical order according to authors' names.

M. A. A.

Pharmacology. By Michael G. Mulinos, M.D., A.B., A.M., Ph.D. With a Foreword by Charles C. Lieb, A.M., M.D. vi plus 482 pages. 22 × 14.5 cm. Oxford University Press, New York, N. Y. 1944. Price, $4.00.

The arrangement set forth in the contents of this book on pharmacology is interesting. After an introduction and a study of pharmacodynamics, the author deals with the chemotherapy of the various types of diseases. Then the systems of the body

are treated with respect to the drugs which act upon them, such as the peripheral nervous system, the central nervous system, the digestive tract, etc. The tenth and final division of the book is devoted to the hormones and the vitamins.

In the foreword to this manual, the author states that there is a crying need for a short Manual of Pharmacology to which the medical student and practitioner can refer for modern concepts of established facts in pharmacology. It is difficult to understand how anyone could make this statement considering the vast array of textbooks and formularies and compendia which are extant on the market for ready reference for the medical student and practitioner. He also recommends the volume primarily to those who intend to practice scientific therapy.

In a review of this book, the reviewer finds many statements which appear to him to be contrary to fact, many drugs which are beyond the pale of rational therapeutics and other statements which are not clear. Missing from the book are such well-established facts as the mechanism of the action of the sulfonamide drugs, newer concepts with regard to the vasodilating properties of organic nitrates including the well-known nitroglycerin, and the mechanism of action of drugs used in the treatment of syphilis. On page 13, the titration of nicotinic acid with tenth-molar sodium hydroxide should be tenth-normal sodium hydroxide. On page 35, the statement that the aliphatic hydrocarbons as a class are hypnotic, analgetic or anesthetic is open to question, for this class contains such hydrocarbons as petrolatum and light liquid petrolatum. On the same page the definition of an organic compound is likewise open to criticism. The reviewer questions the use of nitric acid as a caustic in venereal ulcers and poisoned wounds and also wonders if the oil base in camphor liniment invites friction, as is stated on page 151, or whether the oil base does not eliminate friction and invite inunction. On page 241 the statement is made that chloroform in contact with an open flame produces noxious gases. The reviewer believes that it might be well to inform the medical students that the gases are carbonyl chloride and hydrochloric acid. On page 256, magnesium trisilicate is marked as N. N. R. although it has been official in the Pharmacopoeia for a considerable period of time. On page 257, aromatic spirit of ammonia is said to contain 1.7 to 2.1 per cent of ammonium carbonate. As the Pharmacopoeia states this is ammonia and not ammonium carbonate. There are many other cases too numerous to mention where the author has apparently failed to seek recourse to authentic volumes before stating the effects of various drugs.

It is the reviewer's opinion that this book has possibilities after the statements contrary to fact and typographical errors have been removed and a few additions with regard to the mechanism of action of drugs are included, and that the book may then find its place among the other compendia on pharmacology.

J. C. K., Jr.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

A National Health Service. Presented by the Minister of Health and the Secretary of State for Scotland to Parliament by Command of His Majesty. 85 pages; 23 × 15.5 cm. 1944. The Macmillan Company, New York, N. Y. Price $.75.

Synopsis of Diseases of the Heart and Arteries. By George R. Herrmann, M.S., M.D., Ph.D., F.A.C.P. 516 pages; 20 × 13 cm. 1944. C. V. Mosby Company, St. Louis, Mo. Price, $5.00.

Virus Diseases in Man, Animal and Plant. By GUSTAV SEIFFERT. 332 pages; 23.5 × 15 cm. 1944. Philosophical Library, Inc., 15 E. 40th St., New York 16, N. Y. Price, $5.00.

Elimination Diets and the Patient's Allergies. By ALBERT H. ROWE, M.D. 256 pages; 24 × 15.5 cm. 1944. Lea & Febiger, Philadelphia, Pa. Price, $3.50.

Allergy in Practice. By SAMUEL M. FEINBERG, M.D., with the Collaboration of Oren C. Durham. 798 pages; 23.5 × 16 cm. 1944. The Year Book Publishers, Chicago. Price, $8.00.

A Manual of Physical Therapy. Third Edition, thoroughly revised. By RICHARD KOVACS, M.D. 309 pages; 20.5 × 13.75 cm. 1944. Lea & Febiger, Philadelphia, Pa. Price, $3.25.

Textbook of General Surgery. Fourth Edition. By WARREN H. COLE, M.D., F.A.C.S., and ROBERT ELMAN, M.D. 1118 pages; 23 × 17 cm. D. Appleton-Century Company, Inc., New York 1, N. Y. Price, $10.00.

Inadequate Diets and Nutritional Deficiencies in the United States: Their Prevalence and Significance. Bulletin of the National Research Council, Number 109. 56 pages; 24.5 × 17 cm. 1943 (Nov.). National Research Council—National Academy of Sciences, Washington, D. C. Price, $.50.

Correction. In the review of "Recent Advances in Medicine," March issue, the price of the book was incorrectly given as $5.00. It should have been $5.50.

COLLEGE NEWS NOTES

Additional A.C.P. Members in the Armed Forces

Previously reported in the News Notes Section of this journal were the names of 1,695 Fellows and Associates of the College on active military duty. The following four members bring the total to 1,699, which is about 33 per cent of the total membership:

James A. Bradley
Ralph L. Coffelt
Eugene F. Dubois
Ernest M. Tapp

Dr. Mervin Steves, Special Consultant, U. S. Public Health Service (Reserve), was honorably discharged on April 1, 1944; Major A. Robert Peskin, (MC), AUS, was honorably discharged on December 13, 1943; Lt. Alan Leslie, (MC), USNR, was honorably discharged on December 8, 1943; and Capt. Harry T. Foley, (MC), AUS, was honorably discharged on April 24, 1944.

New Life Members of the College

The following Fellows, listed in the order of subscription, have become Life Members of the College:

Dr. Leon J. Solway, Toronto, Ontario, Can.
Dr. Mack Lipkin, New York, N. Y.
Dr. Martin F. Bruton, Saginaw, Mich.

Gifts to the College Library

Books

David I. Abramson, F.A.C.P., Captain, (MC), AUS—"Vascular Responses in the Extremities of Man in Health and Disease."
Dr. Irvine Page, F.A.C.P., Indianapolis, Ind.—"Hypertension."
Dr. Charles H. Wolohon, F.A.C.P., Washington, D. C.—"The Answer to Your Nerves' Lament."

Reprints

Philip K. Arzt, Associate, Lieutenant, (MC), AUS—1 reprint.
Dr. Andrew L. Banyai, F.A.C.P., Wauwatosa, Wis.—1 reprint.
John L. Ferry, Associate, Captain, (MC), AUS—1 reprint.
Dr. Hyman I. Goldstein, Associate, Camden, N. J.—1 reprint.
Dr. Christopher G. Parnall, F.A.C.P., Rochester, N. Y.—1 reprint.
Lazarus L. Pennock, Associate, Captain, (MC), AUS—1 reprint.
Louis A. Schwartz, Associate, Lieutenant Commander, (MC), USNR—1 reprint.
Dr. Edwin E. Ziegler, F.A.C.P., Bethlehem, Pa.—1 reprint.

Additional gifts to the Library include:

Eli Lilly & Company—"Diabetes Abstracts, 1943," in book form.
The George Washington University School of Medicine—"Studies from the School of Medicine of George Washington University for 1942–43," a bound volume of reprints, many of which were written by members of the College.
Evans Memorial Hospital, Boston, Mass.—31 reprints of publications by members of the staff, several of which are Fellows of the College.

Regional Meeting—Montana and Wyoming

Under the Chairmanship of Dr. Ernest E. Hitchcock, F.A.C.P., Governor for Montana, a Regional Meeting of the American College of Physicians was held at the Rainbow Hotel, Great Falls, Montana, May 6, 1944, with the following program: Dr. Charles Little, F.A.C.P., Great Falls, Mont., "Penicillin and Its Use"; Dr. George E. Baker, F.A.C.P., Casper, Wyo., "Rocky Mountain Spotted Fever" (Illustrated with Kodachrome slides); Dr. M. V. Hargett, F.A.C.P., Surgeon, U. S. Public Health Service, Hamilton, Mont., "Yellow Fever and the War"; Dr. L. L. Howard, F.A.C.S., Great Falls, Mont., "Shock, Use of Blood Plasma"; Dr. Wayne Gordon, F.A.C.P., Billings, Mont., "Diagnosis and Clinical Significance of Gastritis"; Dr. F. M. Schemm, F.A.C.P., Great Falls, Mont., "A Report on the Use of Hypotonic Solutions by Vein."

In the evening there was a cocktail party and dinner. Dr. Hitchcock gave a report on the executive session of the Regents and Governors of the College at Chicago, April 1, 1944, following which there were two formal addresses: Dr. J. P. Ritchey, F.A.C.P., President of the Montana State Medical Association, Missoula, Mont., "Call the Doctor"; Dr. H. C. Watts, F.A.C.P., Fort Harrison, Helena, Mont., "The Veterans Administration and Its Present Medical Problems."

The meeting was attended by a large proportion of the members from the two States as well as by a number of guests.

A.C.P. Regional Meeting, Denver, June 24

A combination of War-Time Graduate Medical Meetings and a Regional Meeting of the American College of Physicians for Colorado, Utah, Arizona, New Mexico, Kansas and Nebraska will be held at Denver, June 22–23–24. June 24 will be devoted wholly to the Regional Meeting of the College. Dr. James J. Waring, F.A.C.P., Regent, is the General Chairman, and Dr. Ward Darley, F.A.C.P., Denver, College Governor for Colorado, Dr. Louis J. Viko, F.A.C.P., Salt Lake City, Governor for Utah, Dr. Fred G. Holmes, F.A.C.P., Phoenix, Governor for Arizona, Dr. Robert O. Brown, F.A.C.P., Santa Fe, Governor for New Mexico, Dr. Harold H. Jones, F.A.C.P., Winfield, Governor for Kansas, and Dr. Warren Thompson, F.A.C.P., Omaha, Governor for Nebraska, constitute the Executive Committee. At the time this announcement goes to press the program has not been completed but acceptances have been received from Dr. Cecil J. Watson, F.A.C.P., Professor of Medicine at the University of Minnesota; Dr. Walter L. Palmer, F.A.C.P., Professor of Medicine at the University of Chicago; Dr. Robert A. Stewart, Director of the Student Health Service Dispensary at the University of California; Lt. Col. Frank B. Queen, F.A.C.P., Bushnell General Hospital, Brigham City, Utah; Lt. Col. George J. Kastlin, F.A.C.P., Bruns General Hospital, Santa Fe, N. M.; and Dr. Ralph A. Kinsella, F.A.C.P., Professor of Medicine at the St. Louis University School of Medicine. Dr. Arthur J. Bedell, Professor Emeritus of Ophthalmology, Albany Medical College, will give the first Edward Jackson Memorial Lecture on "Ophthalmoscopy and the Diagnosis of Human Illness." Dr. Ernest E. Irons, F.A.C.P., Chicago, President of the College, will be present and will speak. The Committee has yet to announce the speaker from the Army on "Reconditioning" and a local speaker on "Rheumatic Fever." Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, will be the chief banquet speaker on the evening of June 23. Mr. Edward R. Loveland, Executive Secretary of the College, and Captain Edward L. Bortz, (MC), USNR, Chairman of the Committee on War-Time Graduate Medical Meetings, both of Philadelphia, are expected to be present and to participate in the program.

A.C.P. Regional Meeting, Vancouver, B. C., September 14–15

Under the Chairmanship of Dr. George F. Strong, F.A.C.P., Vancouver, Regent of the College, and with the assistance of an Executive Committee consisting of Dr.

John W. Scott, F.A.C.P., Governor for the Canadian Southwest, Dr. Samuel M. Poindexter, F.A.C.P., Governor for Idaho, Dr. Homer P. Rush, F.A.C.P., Governor for Oregon, and Dr. Edwin G. Bannick, F.A.C.P., Acting Governor for Washington, a Regional Meeting of the College will be held in Vancouver, September 14–15, for the Canadian Provinces of Alberta, British Columbia, Manitoba and Saskatchewan and for the States of Idaho, Oregon and Washington. Last year the Regional Meeting for this territory was held at Seattle. It is proposed to organize an outstanding program of scientific presentations and to prepare for, at least, one evening devoted to social affairs, with President Ernest E. Irons of Chicago, the principal dinner speaker. On the scientific program will be at least two very competent speakers from the Armed Forces of the United States, who have had actual experience in military medicine in some active theater of the war; likewise, similar medical officers from the Royal Canadian Army.

A cordial invitation will be issued to all members of the College in the territory, all medical officers of the Armed Forces of Canada and the United States stationed in that territory and to other physicians having special interest in the program. Watch for special announcements in these pages later.

Proposed A.C.P. Regional Meeting, Oklahoma City

Plans are underway to conduct a Regional Meeting of the American College of Physicians in Oklahoma City during February, 1945, for the States of Oklahoma, Kansas, Missouri, Nebraska and a portion of Texas. Further announcements will follow.

Report on Registration, A.C.P. Spring Postgraduate Courses

The American College of Physicians conducted the following postgraduate courses during April, 1944:

Course No. 1. General Medicine: University of Michigan Medical School, April 10–15; Dr. Cyrus C. Sturgis, F.A.C.P., Director.

Course No. 2. Clinical Medicine-Hematology: Ohio State University College of Medicine, April 17–22; Dr. Charles A. Doan, F.A.C.P., Director.

Course No. 3. Internal Medicine: Massachusetts General Hospital, April 24–29; Dr. James H. Means, F.A.C.P., Director.

Due to the pressing demand of so many physicians who wished to register for these courses, the maximum facilities were increased for Course No. 1, from 50 to 60; for Course No. 2, from 50 to 60; and for Course No. 3, from 65 to 82. Very few non-members could be accommodated. Physicians were in attendance from 35 States and Canada, with Pennsylvania leading with 33, New York second with 24, Michigan third with 20 and Ohio fourth with 13. An analysis of the registration follows:

Course No.	Fellows	Associates	Non-Members	Total	Civilian	Service
1	47	13	0	60	52	8
2	35	22	3	60	53	7
3	52	20	10	82	73	9
	134	55	13	202	178	24

Tentative Outline, Proposed A.C.P. Postgraduate Courses to Be Held in the Autumn of 1944

The Advisory Committee on Postgraduate Courses of the College is working on the following proposed refresher courses to be held under the auspices of the College

during the autumn of 1944. It should be understood that the program is still in the formative state and there may later be changes in dates as well as in institutions and titles.

COURSE No. 1. GENERAL MEDICINE: University of Oregon School of Medicine, Portland, Oregon; Dr. T. Homer Coffen, Director; October 2–7.

COURSE No. 2. CARDIOLOGY: Massachusetts General Hospital, Boston; Dr. Paul D. White, Director; October 2–7.

COURSE No. 3. SPECIAL PHASES OF INTERNAL MEDICINE: University of Minnesota Medical School, Minneapolis, and the Mayo Foundation, Rochester; Dr. William O'Brien and Dr. E. H. Rynearson, Directors; October 9–21.

COURSE No. 4. ALLERGY: Roosevelt Hospital, New York City; Dr. Robert A. Cooke, Director; October 16–21.

COURSE No. 5. SPECIAL PHASES OF INTERNAL MEDICINE: Chicago Institutions, Chicago; Dr. J. Roscoe Miller, Director; October 23–November 4.

COURSE No. 6. SPECIAL MEDICINE: Philadelphia Institutions, Philadelphia; Dr. Thomas M. McMillan, Director; November 13–24.

Course No. 6 will be very largely a repetition of the very successful course in Special Medicine held in Philadelphia during the autumn of 1943. The course will terminate in a Regional Meeting of the College for the territory embracing Eastern Pennsylvania, New Jersey and Delaware, at Philadelphia on November 24.

By direction of the Board of Regents, due to the great popularity of these courses, registrations from non-members of the College may not be accepted more than three weeks in advance of the opening of any course, and preference shall be given to non-members in the following order: (1) candidates for membership; (2) medical officers in the Armed Forces; (3) physicians preparing for examinations by their certifying boards; (4) all other non-members having adequate background for advanced work. The tuition fee will be based on $20.00 per week for members of the College, and $40.00 per week for non-members, except medical officers in the Armed Forces who will be admitted free.

Major Francis C. Wood, F.A.C.P., (MC), AUS, Chief of Medical Service of the 20th General Hospital, A.P.O. 689, c/o Postmaster, New York, New York, has been appointed by President Ernest E. Irons, a liaison regional director of the College for his theater of the war in order that College interests may be facilitated among its members and for the dissemination of information about the College in India.

Dr. Torald H. Sollmann, F.A.C.P., will retire June 30 as Dean of the School of Medicine and head of the Department of Pharmacology of Western Reserve University, Cleveland, Ohio. Dr. Winfred G. Leutner, President of the University, in announcing Dr. Sollmann's retirement, pointed out that Dr. Sollmann will be free to continue research in pharmacology, a large part of which he was forced to drop when he became Dean of the School of Medicine in 1928, having been on the staff of the medical school for nearly 50 years.

Dr. Arnold D. Welch, research director of Sharpe & Dohme of Philadelphia, has accepted the position as head of the Department of Pharmacology, succeeding Dr. Sollmann in that post. Announcement is expected soon of the appointment of Dr. Sollmann's successor as Dean of the School of Medicine.

TWO A.C.P. FELLOWS COMMENDED

Capt. Walter M. Simpson, F.A.C.P., formerly of Dayton, Ohio, now on duty at the U. S. Naval Hospital, Long Beach, Calif., received the following commendation:

"For meritorious performance of duty while serving as Chief of Medicine, and later as Executive Officer, of the first advanced naval base to be established in the South Pacific area during the period from April 12, 1942, to November 1, 1943. Capt. Simpson reflected great credit on himself by his outstanding professional ability, leadership and keen judgment. As Liaison Officer he dealt with officials in foreign nations with tact and diplomacy, thus contributing materially to the harmonious relations with foreign nationals. As President of the Malaria Control Commission and Sanitary Commission, he organized and initiated the measures which led to the control of tropical diseases. His courageous conduct was in keeping with the highest traditions of the United States Naval Service."

Commander Alphonse McMahon, F.A.C.P., formerly of St. Louis, Mo., received the following citation:

"For meritorious performance of duty while serving at the first advanced naval base hospital to be established in the South Pacific area during the period from April 12, 1942, to October 21, 1943. Commander McMahon reflected great credit on himself by his outstanding professional ability and keen judgment, particularly in the management of war wounds and in the treatment of tropical diseases. His long experience as a teacher of medicine and his effective leadership in the instruction of young medical officers contributed materially to the success of our operations and was in keeping with the highest traditions of the United States Naval Service."

Examinations by Certifying Boards

American Board of Internal Medicine, William A. Werrell, M.D., Assistant Secretary-Treasurer, 1301 University Avenue, Madison 5, Wisconsin.

Written Examinations: October 16, 1944, in various centers throughout the United States; also available to candidates in military and naval services at certain of their stations, with permission of their medical commanding officers. All applications for civilian candidates should be filed by August 15, 1944. Every effort will be made to accommodate candidates in the Service, regardless of the closing date for the acceptance of applications.

Oral Examinations: Consult Assistant Secretary-Treasurer; oral examinations will probably be given just preceding the annual meeting of the American College of Physicians in the early spring of 1945, and also just preceding the annual meeting of the American Medical Association in the late spring of 1945. If the Board finds it possible to conduct regional examinations during 1944, an announcement will appear in the Annals of Internal Medicine and the Journal of the American Medical Association.

American Board of Dermatology and Syphilology, C. Guy Lane, M.D., Secretary, 416 Marlboro Street, Boston, Massachusetts.

Consult the Secretary concerning examination schedule for autumn of 1944 and spring of 1945.

American Board of Pediatrics, C. A. Aldrich, M.D., Secretary, 115½ First Avenue, S.W., Rochester, Minnesota.

Written Examination: September 22, 1944, locally under monitors.

Oral Examinations: St. Louis, Missouri, November 8–9, 1944, and New York City, December 9–10, 1944. Closing date for filing applications, July 8, 1944.

American Board of Pathology, F. W. Hartman, M.D., Secretary-Treasurer, Henry Ford Hospital, Detroit, Michigan.

Consult the Secretary-Treasurer for future schedule.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, Walter Freeman, M.D. Secretary, 1028 Connecticut Avenue, N.W., Washington, D.C.

Consult the Secretary for future schedule. At last advice, this Board will schedule an examination in New York City about the middle of December, 1944. However, the dates for both the written and oral examinations will not be set until late autumn or early winter.

AMERICAN BOARD OF RADIOLOGY, B. R. Kirklin, M.D., Secretary, Mayo Clinic, Rochester, Minnesota.

This Board conducts only a general oral examination. Next examination will be held in Chicago, Illinois, September 22–23–24, 1944.

INSTITUTO NACIONAL DE CARDIOLOGIA OF MEXICO

The Government of Mexico inaugurated the new National Institute of Cardiology at Mexico City, April 18–22, 1944. Dr. Ignacio Chavez, F.A.C.P., of Mexico City, will be the Director of the Institute.

The Federal Government of Mexico officially invited as guests to the inaugural ceremonies the following members of the College from the United States, whose presentations are also named:

Dr. Carl J. Wiggers, F.A.C.P., Cleveland, Ohio, "Laboratory Studies of Clinical Problems in Cardiology";

Dr. Louis N. Katz, F.A.C.P., Chicago, Ill., "The Factors Controlling the Coronary Circulation" and "The Value of the Chest Leads CF_2, CF_4, and CF_5 in the Evaluation of Heart Strain";

Dr. Frederick A. Willius, F.A.C.P., Rochester, Minn., "A Consideration of Certain Unsolved Problems in Cardiology";

Dr. Samuel A. Levine, F.A.C.P., Boston, Mass., "Some Observations Concerning Cardiac Murmurs and Their Mode of Transmission" and "Some Harmful Effects of Recumbency in the Treatment of Heart Disease";

Dr. Paul D. White, F.A.C.P., Boston, Mass., "Man Himself the Chief Problem in Cardiology," "The Evolution of Our Knowledge of Coronary Heart Disease," and "Studies of Cases of Hypertension Treated by Lumbodorsal Splanchnic Resection";

Dr. Frank N. Wilson, F.A.C.P., Ann Arbor, Mich., "The Electrocardiographic Diagnosis of Myocardial Infarction Complicated by Bundle Branch Block";

Dr. Harold B. Pardee, F.A.C.P., New York, N. Y., "Influence of the Situation and Extent of Myocardial Infarction upon Certain Features of the Electrocardiogram";

Dr. Charles C. Wolferth, F.A.C.P., Philadelphia, Pa., "Negative Displacement of the RS–T Segment in the Electrocardiogram and Its Relationships to Positive Replacement";

Dr. William D. Stroud, F.A.C.P., Philadelphia, Pa., "The Modern Use of Digitalis" and "Coronary Artery Disease";

Dr. George R. Herrmann, F.A.C.P., Galveston, Tex., "Digitalis Intoxication with Special Reference to Increasing Frequency" and "Studies on the Mechanism of Supraventricular Paroxysmal Tachycardia with Heart Block";

Dr. William J. Kerr, F.A.C.P., San Francisco, Calif., "The Treatment of Angina Pectoris" and "The Clinical Use of the Symballophone."

Dr. Chavez also delivered the following paper: "Contribución al Conocimiento del Sindrome de Wolff-Parkinson-White."

The Institute is a magnificent new hospital, which is almost ready to receive patients. Its equipment is entirely up-to-date in all respects. The American delegation was entertained by Ambassador George Messersmith and a dinner was also tendered the group by Dr. Francisco de P. Miranda, F.A.C.P., College Governor for Mexico, Dr. Chavez and Dr. Salvador Zubiran, F.A.C.P., all of Mexico City.

Committee on Post-War Planning for Medical Service

The Committee on Post-War Planning for Medical Service of the American College of Physicians met with the central Committee consisting of representatives from the American College of Surgeons and the American Medical Association, at the Waldorf-Astoria Hotel, New York City, Saturday, April 29, Dr. Roger I. Lee, F.A.C.P., acting as Chairman. The meeting was given over largely to general discussion and to a report from Colonel Luth on returns from a questionnaire which had been distributed to 3,000 officers on active duty in the three military services. When the findings have been more conclusively recorded with regard to the sort of training, the length of training and the type of specialty training desired, the facts will be published. The Committee voted to send a questionnaire to every medical officer in the Armed Forces, with the coöperation of the three Surgeons General.

Among subjects discussed at length was the desirability of requesting the Committee on Procurement and Assignment to intercede in behalf of medical schools for an early release of medical teachers. A sub-committee of Dr. Walter W. Palmer, Chairman, Dr. Alan Gregg and Dr. W. C. Rappleye was appointed to encourage the medical schools to supply lists of teachers needed, this list to be presented to the Committee on Procurement and Assignment at an early date. The Committee on Post-War Planning will meet with the Committee on Procurement and Assignment in the near future.

The following officers of the medical board of the Philadelphia General Hospital were reëlected at a recent meeting:

Dr. Russell S. Boles, F.A.C.P., President
Dr. Samuel B. Hadden, F.A.C.P., Secretary
Dr. Lawrence W. Smith, F.A.C.P., Treasurer.

At the regular monthly scientific meeting of the Macon County (Illinois) Medical Society held at Decatur, April 18, 1944, Dr. LeRoy H. Sloan, F.A.C.P., Professor of Medicine at the University of Illinois and Regent of the American College of Physicians, conducted a Clinico-Hematological Conference. Associated with him was Dr. L. R. Limarzi, Assistant Professor of Medicine at the University of Illinois. Dr. Sloan's subject was "Blood Dyscrasias." Dr. Cecil M. Jack, F.A.C.P., Governor of the College for Southern Illinois, was Director of the Clinic.

Dr. R. Manning Clarke, F.A.C.P., formerly Clinical Professor of Medicine at the College of Medical Evangelists, Los Angeles, has recently been appointed to the staff of the Department of Medicine of the Woman's Medical College of Pennsylvania, where he is serving in the same capacity. Dr. Clarke maintains an office at 401 West Jersey Trust Bldg., Camden, N. J.

Lt. Col. Louis Laplace, (MC), AUS, F.A.C.P., formerly of Philadelphia, has been assigned recently as Chief of the Medical Service, Glennan General Hospital, Okmulgee, Okla.

Dr. Richard K. Richards, F.A.C.P., Chicago, addressed the Science Department of the University of Illinois at Urbana on "Medical Aspects of Water Metabolism in Man," April 18.

Dr. Henry H. Turner, F.A.C.P., Oklahoma City, spent the first two weeks of April in Mexico City to lecture on Endocrinology before the National University Medical School and the National Academy.

Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, is the author of a special article on "Medicine Versus Socialized Medicine," which was published in the April, 1944, issue of the Journal of the Oklahoma State Medical Association.

Captain Leon J. Galinsky, (MC), AUS (Associate), now stationed at Camp Crowder, Mo., on May 5 made a donation of $20.00 to the American College of Physicians Postgraduate Fund, which is acknowledged with gratitude.

The Hollywood Presbyterian (Olmsted Memorial) Hospital, Hollywood, Calif., recently announced its fourth annual series of lecture-conferences on the general topic, "Diagnosis without Tools," to be given by Dr. Ross Moore, F.A.C.P., Chief of the Neuropsychiatric Department. The especial topic for 1944 series is "Diagnostic Self Study"; the subject for June 22 will be "The Physical and Physiological Bases for Diagnostic Self Study"; for June 29, "The Mental and Environmental Bases for Diagnostic Self Study"; and for July 6, "The Self Study Itself."

Dr. James D. Trask, 1942 Phillips Medalist of the American College of Physicians and one of America's most famous fighters in the war against infantile paralysis, was posthumously honored during May when a Liberty ship named in his honor was launched at the Bethlehem-Fairfield shipyards in Baltimore. The ship was christened by his widow, with prominent scientists from Yale University and Johns Hopkins University present at the ceremonies.

Dr. Trask, who died in Chicago on May 24, 1942, while working for an Army Medical Commission under an appointment as consultant to the Secretary of War, became internationally known for his work in infantile paralysis, a large part of it done with his associate, Dr. John R. Paul of Yale University, who also received the Phillips Medal of the American College of Physicians. The two men who helped found the Yale Poliomyelitis Commission in 1931 after an epidemic of infantile paralysis swept Connecticut, made an outstanding team in the study of the disease. In recognition of their work, Dr. Trask and Dr. Paul received the first grant made by the Committee on Virus Research of the National Foundation for Infantile Paralysis after it was organized in 1938.

Baruch Committee on Physical Medicine Makes Donation for Teaching and Research in Physical Medicine

On April 27, 1944, the Baruch Committee on Physical Medicine announced that after a scientific exploration of the possibilities of the subject with special reference to its value in the rehabilitation of the wounded and ill men discharged from the Armed Forces—casualties of war—Mr. Bernard M. Baruch had given a sum of $1,100,000.00 to be used for the teaching of and research in physical medicine. The

program will be inaugurated by an administrative board under the Chairmanship of Dr. Ray Lyman Wilbur, Chancellor of Stanford University. Dr. Frank H. Krusen, F.A.C.P., of Rochester, Minn., was Director of the Committee making the investigation. The chief needs for proper development of physical medicine, the report avers, are: (1) an adequate supply of physicians who can teach and use physical medicine; (2) more extensive basic research in physical medicine; and (3) proper use of physical medicine in relation to wartime rehabilitation and peacetime physical preparedness. The immediate program includes (1) organization of a central office to coördinate and promote teaching and research in physical medicine; (2) establishment of teaching and research centers of physical medicine at certain interested and well-qualified medical schools; (3) establishment of Fellowships in physical medicine; (4) promotion of the teaching of physical medicine in all medical schools; (5) preparation of reports by the Committee; and (6) promotion of wartime and post-war physical rehabilitation.

The eventual program includes promotion of certain general projects for advancement of physical medicine and the adoption of certain resolutions concerning projects on which the Committee looks with favor.

It was announced that Columbia University College of Physicians and Surgeons will receive $400,000.00 for the establishment of a key center of research and teaching of physical medicine with particular reference to its application for returning veterans; that New York University College of Medicine will receive $250,000.00 to establish a center for teaching and special research in preventive and manipulative structural mechanics of physical medicine; that the Medical College of Virginia shall receive $250,000.00 to establish a center for teaching and research with particular reference to hydrology, climatology and spa therapy; that $100,000.00 shall be assigned to selected medical schools to develop an immediate program for the physical rehabilitation of war casualties and those injured in industry; that $100,000.00 shall be assigned to the establishment of fellowships and residencies for the benefit of qualified physicians or other scientists who are selected to be trained in this field.

Several Fellows of the American College of Physicians have been selected to serve on various committees.

Lt. Col. Thomas Fitz-Hugh, Jr., (MC), AUS, F.A.C.P., who spent nine months overseas but was returned some months ago to the McGuire General Hospital, Richmond, Va., was assigned during May to the Third Service Command, Baltimore, as medical consultant.

Major D. Sergeant Pepper, (MC), AUS, F.A.C.P., who also has been on overseas duty, is now Assistant Chief of Medicine at the McGuire General Hospital.

At the meeting of the Texas State Heart Association, April 20, 1944, Dr. Victor Schulze, F.A.C.P., San Angelo, was elected President, Dr. F. E. Hudson, F.A.C.P., Stamford, was elected Vice-President and Dr. B. W. Whiting, F.A.C.P., Wichita Falls, was elected Secretary-Treasurer.

At the 17th annual meeting of the Medical Society of New Jersey at Atlantic City, April 26, 1944, Dr. Louis L. Perkel, F.A.C.P., Jersey City, was elected Secretary of the Section on Gastro-enterology. Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, retiring Chairman of this Section, presented a paper on "Common Disorders of the Digestive Tract," which was discussed by Dr. Hyman I. Goldstein, (Associate), Camden, who also discussed the paper on "Metabolic Disturbances Associated with Cancer of the Gastrointestinal Tract," presented by Dr. George T. Pack, New York

City. Captain J. Edward Berk, (MC), AUS, F.A.C.P., of Fort Dix, gave a paper on "Gastrointestinal Problems in the Army."

Dr. Harry P. Thomas, (Associate), has recently been appointed Superintendent of the Woodmen of the World War Memorial Hospital at San Antonio, Tex.

The Marcelle Cosmetic Company of Chicago has arranged for $500.00 to be given annually for five successive years to the American College of Allergists for research in the field of allergy. A similar amount has been offered to the American Academy of Allergy.

Dr. Ralph Bowen, F.A.C.P., Houston, Tex., was elected President of the Southwest Allergy Forum recently. This Forum will hold its 1945 meeting at New Orleans, April 5–6.

Dr. Henry L. Bockus, F.A.C.P., Professor of Gastro-enterology, University of Pennsylvania Graduate School of Medicine, delivered a paper on "Common Mistakes in the Diagnosis and Treatment of Digestive Tract Disorders," before the Hartford Medical Society, Hartford, Conn., on April 3, 1944.

The American Psychiatric Association, which has a membership of more than 3,000 members and was founded in Philadelphia 100 years ago, held its Centennial Meeting in Philadelphia, May 15–18, 1944, under the Presidency of Dr. Edward A. Strecker, F.A.C.P., Philadelphia. The transition from war to peace and the rehabilitation of the war's wounded was a major theme. A section was devoted to Psychiatry and the U. S. Army and another section to Psychiatry and the U. S. Navy.

Dr. Henry S. Houghton, F.A.C.P., for many years Acting Director of the Peiping Union Medical College in China, is reported to have been interned on the first day of the war between Japan and the United States and to have been placed in solitary confinement.

The Hospital for Joint Diseases, 1919 Madison Avenue, New York City, an institution approved by the American Medical Association for general internships and residencies and by the American College of Surgeons as meeting its standards, offers general rotating internships to fill four vacancies October 1, 1944, and eight vacancies to begin July 1, 1945, each for nine months. One-half of the number appointed may be permitted to continue for another nine months as junior residents, and thereafter, one-half of the number of junior residents may be continued for another nine months as senior residents, in accordance with the Allocation Plan of the Procurement and Assignment Service. The Hospital will provide maintenance, uniforms and a stipend of $25.00 a month.

Under the Presidency of Dr. Eugene P. Pendergrass, F.A.C.P., the Philadelphia County Medical Society held its 9th annual Postgraduate Institute at the Bellevue-Stratford Hotel, Philadelphia, May 2–5. Dr. Charles L. Brown, F.A.C.P., is the President-Elect. Dr. George P. Muller, F.A.C.S., is Director of the Postgraduate Institute Commission. Dr. T. Grier Miller, F.A.C.P., is Chairman of the Committee on Medical Education and Scientific Program and Dr. Stanley P. Reimann, F.A.C.P., is the Chairman of the Committee on Scientific Exhibits. The general

theme of the Institute was "Modern Diagnosis and Treatment." Among speakers on the scientific program were: Dr. Martin J. Sokoloff, F.A.C.P., "Medical Treatment of Tuberculosis"; Lt. Comdr. Joseph F. Hughes, (MC), USNR, (Associate), Philadelphia Naval Hospital, "Electroencephalography"; Dr. John Lansbury, F.A.C.P., "The Relation of Fluorine to the Prevention of Dental Caries in Children"; Dr. Ella Roberts, (Associate), "Sulfonamide Prophylaxis in Rheumatic Fever"; Dr. Malcolm W. Miller, F.A.C.P., "Intractable Asthma"; Dr. Harold W. Jones, F.A.C.P., "Hemorrhagic Blood Dyscrasias"; Dr. Lowell Erf, F.A.C.P., "Blood and Blood Plasma"; Dr. Harrison F. Flippin, F.A.C.P., "Post-Operative Pulmonary Complications—From the Standpoint of the Internist"; Dr. G. Harlan Wells, F.A.C.P., "Post-Operative Pulmonary Complications—Medical Aspects"; Dr. Leandro Tocantins, (Associate) "Combined Use of Heparin and Dicoumarin for Thromboembolic Disorders"; Dr Thomas M. McMillan, F.A.C.P., "Diagnosis of Coronary Occlusion"; Dr. William G Leaman, Jr., F.A.C.P., "Management of Acute Coronary Occlusion"; Dr. William D. Stroud, F.A.C.P., "Selection and Use of Digitalis Glucosides"; Dr. Thomas M. Durant, F.A.C.P., "Bedside Diagnosis and Treatment of Arrhythmias"; Dr. George Morris Piersol, F.A.C.P., "Rehabilitation and Its Relation to Physical Therapy"; Comdr. Thomas N. Spessard, (MC), USNR, (Associate), Philadelphia Naval Hospital, "Psychiatry in a Naval Hospital"; Dr. T. Grier Miller, F.A.C.P., "Principles of Peptic Ulcer Management"; Dr. Russell S. Boles, F.A.C.P., "Medical Management of the Complications of Peptic Ulcer"; Dr. Henry L. Bockus, F.A.C.P., "Regional Ileitis"; Dr. Edward Weiss, F.A.C.P., "Psychosomatic Aspects of Gastro-enterology From the Standpoint of the Internist"; Dr. William A. Swalm, F.A.C.P., "Laboratory Aids in Gastrointestinal Disorders."

At a luncheon on the opening day of the meeting, guest speakers included Dr. A. Hamilton Stewart, F.A.C.P., Secretary of Health, Commonwealth of Pennsylvania; Dr. Rufus S. Reeves, F.A.C.P., Director of the Department of Public Health, City of Philadelphia; and Dr. Augustus S. Kech, F.A.C.P., President of the Medical Society of the State of Pennsylvania. At the annual dinner meeting of the Institute, Dr. Edward A. Strecker, F.A.C.P., was the chief speaker, his subject being "Psychiatric Ramblings."

Dr. Russell L. Haden, F.A.C.P., Cleveland, addressed the Fulton County Medical Society at Atlanta, Ga., March 30, on Leukemia.

The 65th annual meeting of the Louisiana State Medical Society was held at New Orleans, April 24–26, under the Presidency of Dr. Charles C. deGravelles, F.A.C.P., New Iberia. Dr. Felix J. Underwood, Jackson, Miss., delivered the annual oration at the President's dinner.

At the annual meeting of the Nebraska State Medical Association, Omaha, May 1–4, Col. Edgar V. Allen, (MC), AUS, F.A.C.P., presented a paper on "Functional Somatic Disorders in the Army," from the standpoint of the internist, and Lt. Col. Clarke H. Barnacle, (MC), AUS, F.A.C.P., discussed the same subject from the viewpoint of the psychiatrist.

The Medical Society of the State of North Carolina held its 91st annual session at Pinehurst, May 1–3, under the Presidency of Dr. James W. Vernon, F.A.C.P., Morganton. Dr. James E. Paullin, F.A.C.P., was a guest speaker, his subject, "Medical Planning for the Post-War Period."

Dr. Edward L. Turner, F.A.C.P., Nashville, Tenn., was a guest speaker at the 98th annual meeting of the Ohio State Medical Association at Columbus, May 2–4, his subject being "The Dysenteries."

Dr. Edward Weiss, F.A.C.P., Philadelphia, Pa., has been named by the National Committee for Mental Hygiene director of a fund for research in psychosomatic medicine to stimulate and subsidize research in the psychosomatic aspects of the diseases chiefly responsible for disability and death. Lt. Col. William C. Menninger, (MC), AUS, F.A.C.P., is a member of the Committee which will pass upon projects.

At the annual meeting of the Medical Society of the State of New York at Hotel Pennsylvania, New York City, May 8–11, the following were among guest speakers: Dr. Lewis M. Hurxthal, F.A.C.P., Boston, "Practical Management of Certain Endocrine Disorders"; Dr. Sara M. Jordan, F.A.C.P., Boston, "Medical Aspects of Recalcitrant and Complicated Ulcer"; Dr. Irvine H. Page, F.A.C.P., Indianapolis, "Recent Advances in Etiology, Diagnosis and Treatment of Essential Hypertension."

The State Medical Association of Texas, because of war conditions, has divided its annual meeting into four sections. Among the out-of-state speakers on the program at Fort Worth, April 20–21, was Lt. Col. Oza J. LaBarge, (MC), AUS, F.A.C.P., whose subject was "Virus Disease of the Respiratory Tract."

The American Diabetes Association held its 4th annual meeting at Chicago, June 11. Dr. Cecil Striker, F.A.C.P., Cincinnati, is the Secretary.

Dr. Paul D. White, F.A.C.P., Boston, delivered the oration in medicine, "The Evolution of Our Knowledge of Coronary Heart Disease," before the 104th annual session of the Illinois State Medical Society at Chicago, May 16–18.

Dr. Italo F. Volini, F.A.C.P., Chicago, has been appointed Dean of the Loyola University School of Medicine for the duration of the war. He takes the place of Comdr. Francis J. Braceland, (MC), USNR, F.A.C.P., now on leave.

Dr. Howard Karsner, F.A.C.P., Director of the Institute of Pathology, Western Reserve University, Cleveland, delivered the first Frederick R. Zeit Lecture at Northwestern University Medical School, May 18, on "Hepatic Cirrhosis."

The Massachusetts Medical Society held its 163rd annual meeting at Boston, May 22–24, under the Presidency of Dr. Roger I. Lee, F.A.C.P., Boston. Dr. Walter C. Alvarez, F.A.C.P., Rochester, Minn., was among the guest speakers, his subject being "Abdominal Pain."

Lt. Col. Howard A. Rusk, (MC), AUS, F.A.C.P., delivered the banquet address, "Convalescent Rehabilitation Program in the Army," before the Kansas Medical Society at Topeka, May 10–11.

Dr. Jerome E. Andes, F.A.C.P., has resigned, because of ill health, as Director of the University Health Service and Associate Professor of Medicine, West Virginia University School of Medicine, Morgantown.

Comdr. Alphonse McMahon, (MC), USNR, F.A.C.P., addressed the 77th annual meeting of the West Virginia State Medical Association at Wheeling, May 15–16, on "Medicine in the South Pacific." He also addressed the Victory dinner meeting of the Association on "Native Customs of the South Pacific."

At the annual meeting of the Association of American Physicians at Atlantic City during May, Dr. Warfield T. Longcope, F.A.C.P., Baltimore, was elected President; Dr. O. H. Perry Pepper, F.A.C.P., Philadelphia, was elected Vice-President; Dr. Joseph T. Wearn, F.A.C.P., Cleveland, was elected Secretary; Dr. Fred M. Smith, F.A.C.P., Iowa City, was elected Recorder; and Dr. William S. McCann, F.A.C.P., Rochester, N. Y., was elected Treasurer.

Dr. Oliver C. Melson, F.A.C.P., Little Rock, College Governor for Arkansas, has been appointed a member of the Council of the Southern Medical Association for a term of five years.

Dr. John H. Musser, F.A.C.P., New Orleans, has been elected a trustee of the University of Pennsylvania for a 10-year term.

Dr. Ralph L. Shanno, F.A.C.P., Forty Fort, Pa., recently addressed the Wyoming County (Pa.) Medical Society at Tunkhannock on "The Diagnosis of Heart Disease" and the Columbia County (Pa.) Medical Society at Bloomsburg on "Coronary Disease."

Dr. Joseph C. Doane, F.A.C.P., Philadelphia, addressed Station Hospital Staff at Fort Dix, N. J., on March 2, 1944. The subject was "Peripheral Vascular Disease with Special Reference to Anti-coagulants." Dr. Doane is scheduled to speak on the same subject at the Annual Meeting of The Maine Medical Association at the Hotel Samoset, Rockland, Maine, on June 26, 1944.

The Committee on Medical Education of The New York Academy of Medicine announces that a Fellowship in Research provided by Dr. Charles Mayer of New York City has been awarded to Dr. Philip Handler of Duke University.

WAR-TIME GRADUATE MEDICAL MEETINGS

REGION No. 4 (Eastern Pennsylvania, Delaware, New Jersey)—Dr. B. P. Widmann, Chairman; Dr. J. S. Rodman, Dr. S. P. Reimann

Station Hospital, Fort Monmouth, New Jersey

June 21. Acute Glomerulo-nephritis. Dr. Geo. Morris Piersol.
June 28. Malignancy as Seen in Armed Forces. Dr. Stanley P. Reimann

Station Hospital, Indiantown Gap, Pennsylvania

June 21. Complications Occurring in Diabetes. Dr. David W. Kramer
June 28. The Relationship of Pain and Tenderness to Body Mechanics. Dr. John C. Howell

REGION No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. G. L. Weller

Station Hospital, Langley Field, Virginia

June 20. Treatment of Cardiovascular Emergencies. Dr. William B. Porter

U. S. Naval Hospital and U. S. Naval Academy Dispensary, Annapolis, Maryland

June 16. Maxillo-facial Surgery. Dr. John Staige Davis

REGION No. 9 (Michigan)—Dr. J. M. Robb, Chairman; Dr. A. D. McAlpine, Dr. R. H. Lyons

Station Hospital, Fort Custer, Michigan

June 21. Convalescent and Rehabilitation Program. Major D. W. McCormick
Malaria Control Demonstration and Field Expedients of Military Sanitation. Post Sanitary Corps Instructor
Demonstration of Disposition Board Procedure. Disposition Board
Low Back Pain. Major D. W. McCormick

Percy Jones General Hospital and Fort Custer, Battle Creek, Michigan

June 21. Allergic States
a. Bronchial Asthma—Migraine
b. Dermatological and Other Allergic States

July 5. Head and Spine Injuries
a. Methods of diagnosis and localization
b. Do's and don't's before the patient reaches the special surgeon

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. L. H. Sloan, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole

Mayo General Hospital, Galesburg, Illinois

June 21. Heart Disease
a. Rheumatic Heart Disease
b. Subacute Bacterial Endocarditis

July 5. Effects of Cold and Dampness
Frostbite, Immersion Feet, and Allied Conditions
The Raynaud's Syndrome—Mechanism and Treatment

Vaughan General Hospital, Hines, Illinois

June 21. Peripheral Vascular Diseases
a. Diagnosis and Conservative Treatment
b. Surgical Treatment

July 5. Arthritis { Rheumatoid—Acute Rheumatic Fever / Osteo-arthritis }
a. Other Bone Diseases

Camp Ellis, Illinois

June 21. Diseases of the Kidneys, Uro-genital Tract
a. Diseases of the Kidneys—Edema
b. Surgical Considerations

July 5. Blood Dyscrasias
a. Acute and Chronic

Camp McCoy, Wisconsin

June 21. High Blood Pressure
- *a.* Pathological—Physiological Basis—Conservative Therapy—Renal Extracts
- *b.* The Surgical Treatment

July 5. Laboratory Diagnosis and Its Relationship to Treatment
- *a.* Hypoproteinemia—Alkalosis—Acidosis—Dehydration—Electrolytic Balance

Camp Grant, Illinois

June 21. Conditions Affecting Glucose Metabolism
- *a.* Endocrine—Pituitary—Thyroid—Adrenal—Pancreatic
- *b.* Renal, Alimentary, Hepatic. Differential Diagnosis and Treatment

July 5. Orthopedic Problems of General Interest
- *a.* Low Back Pain—Foot and Knee Strain—March Fracture, etc.

Truax Field, Wisconsin

June 21. Diseases of the Intestinal Tract
- *a.* Regional Ileitis, Colitis, Diverticulitis, Diagnosis and Treatment
- *b.* Dysentery—Army and Bacillary
- *c.* Malignancies

July 5. Symposium on Organic Neurology
- *a.* Central and Peripheral

Scott Field, Illinois

June 21. Dermatological Diseases

Clinic with presentation of cases and slides. Diagnosis and Treatment.
- *a.* The Less Common Venereal Diseases

Lymphogranuloma Venereum, Granuloma Inguinale, Chancroid, Yaws.

July 5. Psychiatry, Psychoneurosis, Neurocirculatory Asthenia, Malingering, etc.

Chanute Field, Rantoul, Illinois

June 21. Malignancies in the Army Age Group
- *a.* Melanomata
- *b.* Teratomata
- *c.* Lymphoblastomata

July 5. Endocrinology

Addison's Disease, Adrenal Cortex in Shock, Parathyroid Tetany, Traumatic Hypogonadism, Hypothyroidism, Hyperthyroidism, Post Traumatic Pituitary Syndrosis

REGION No. 19 (Colorado, Utah)—Dr. J. J. Waring, Chairman; Dr. J. W. Amesse, Dr. C. F. Hegner

Denver, Colorado

June 22–24. Combined Regional Meeting of the American College of Physicians and War-Time Graduate Medical Meeting

REGION No. 24 (Southern California)—Dr. B. O. Raulston, Dr. W. A. Morrison. (This meeting has been arranged by Captain Harry P. Schenck, National Con-

sultant in Otolaryngology for the War-Time Graduate Medical Meetings, U. S. Naval Hospital, Santa Margarita Ranch, Oceanside, California.)

U. S. Naval Hospital, Santa Margarita Ranch, Oceanside, California

June 21. SYMPOSIUM ON REHABILITATION

Ward rounds, demonstrations, dry clinics
Inspection of clinical facilities
Symposium: REHABILITATION
General Surgery—Commander E. L. Calhoun
Orthopedics—Commander J. D. MacPherson
Psychiatry—Lieutenant Commander J. H. Nichols
Otolaryngology—Captain Harry P. Schenck

(Note: For more detailed information concerning these meetings, contact local committees.)

Somewhere in New Guinea: Lieut. Colonel Charles R. Castlen, M.C., F.A.C.P., as Commanding Officer of a Station Hospital in New Guinea, takes great pride not only in his unit's fine record in caring for the sick and wounded, but also in the remarkable fact that he and members of his organization—doctors, dentists, nurses, technicians and clerks—actually built the hospital, from foundation to roof.

This up-to-date military hospital, which rose from the ruins of a deserted native mission in the green foothills of the Owen Stanley mountains, in view of the blue-green waters of a tropical sea, stands as a monument to the devotion to duty and ingenuity exercised by Medical Department personnel in carrying out their tremendous task of caring for battle casualties and victims of tropical disease endemic to this humid island-continent.

Arriving in New Guinea last September, after a brief stop in Australia, Col. Castlen and his staff found only the tattered remains of a Papuan mission, surrounded by high kunai grass, at the site assigned for the erection of the hospital.

Immediately, qualification records of all personnel in the unit were consulted, preparatory to organization of "construction crews" to begin work on the project. Men who had had experience with hammer and saw became carpenters; those who as boys had tinkered with electrical "gadgets" became electricians—and on through the category of building trades until a complete construction gang—from superintendent to water boy—had been formed.

Each department head was placed in charge of construction of his respective section of the hospital and thus a spirit of competition developed, with each group trying to do a better job than the others.

So, in a remarkably short time, considering the inexperience of the workers, the hospital was complete and in operation; and today this modern, fully equipped unit is doing a notable job serving sick and wounded soldiers evacuated from all parts of New Guinea and other islands of the Southwest Pacific.

FINANCIAL REPORT FOR THE YEAR 1943

At a meeting of the Board of Regents, Chicago, April 1, 1944, full and detailed financial statements of the College for the year 1943 were presented, as certified by the auditors. Selected portions of the report are herewith published.

EXECUTIVE SECRETARY'S SUMMARY REPORT TO TREASURER AND FINANCE COMMITTEE

1943

The Auditor's Report on the examination of the accounts of the College is hereto attached. The 1943 net increase in surplus (General and Endowment Funds) amounted to $27,902.20.

1940 Balance	$27,315.51	1942 Balance	$27,988.83
1941 Balance	25,641.29	1943 Balance	27,902.20

The following is a condensed, comparative review for the past two years:

	1942		1943	
GENERAL FUND, Balance, January 1		$166,323.61		$190,569.76
Operating Net Income	$24,705.05		$20,300.33	
Losses on Investments			— 283.61	
Profit on Investments	91.10			
Net Increase for Year		24,796.15		20,016.72
		$191,119.76		$210,586.48
Transfers to Endowment Fund:				
Initiation Fees, Life Members		— 550.00		— 2,510.00
PRINCIPAL, GENERAL FUND, December 31		$190,569.76		$208,076.48
ENDOWMENT FUND, Balance, January 1		$132,586.38		$136,329.06
Additions during year:				
Life Member Subscriptions	$ 2,508.00		$ 7,285.00	
Transfers from General Fund ...	550.00	3,058.00	2,510.00	9,795.00
Profit on Investment (net of losses)		684.68		600.48
PRINCIPAL, ENDOWMENT FUND, December 31		$136,329.06		$146,724.54
TOTAL, BOTH FUNDS, December 31		$326,898.82		$354,801.02
TOTAL INCREASE, BOTH FUNDS		$ 27,988.83		$ 27,902.20

The last page of this report shows a summary of the estimated income and expenditures as approved by the Board of Regents, November 20, 1943, for the year 1944; to wit, a total estimated income of $92,910.00 and total estimated expenditures of $81,115.00, with an estimated balance of $11,795.00.

Respectfully submitted,
(Signed) E. R. LOVELAND
Executive Secretary

March 1, 1944

EXHIBIT "A"

GENERAL FUND

Assets and Liabilities, December 31, 1943

Current Assets			
Cash in bank and on hand			$ 41,537.48
Accounts Receivable	$	55.33	
Drexel & Co.		450.62	
Advertising		1,350.96	
American Air Lines		425.00	
Postgraduate Courses		20.00	2,301.91
Inventory of Keys, Pledges and Frames			363.00
Accrued Income on General Fund Investments....	$	583.13	
Accrued Income on Endowment Fund Investments		1,357.09	1,940.22
Investments at Book Value (Cost).....			115,903.16
Insurance Deposit			555.00 $162,600.77

Fund Assets

College Headquarters Real Estate	$57,728.45		
Less Reserve for Depreciation	7,000.00	50,728.45	
Investment, Real Estate 404–12 S. 42nd St.		9,170.50	
Furniture and Equipment, at cost	$11,111.20		
Less Reserve for Depreciation	7,858.04	3,253.16	63,152.11
Total Assets, General Fund			$225,752.88

Liabilities

Current

Accounts Payable, Miscellaneous		$ 90.14	
Deferred Income			
Phila. Postgraduate Fund	$ 2,284.30		
Advanced Subscriptions ANNALS OF INTERNAL MED. (Vols. 20–21–22–23–24–25)	15,301.96	17,586.26	
Total Liabilities			17,676.40
General Fund			208,076.48
			$225,752.88

ENDOWMENT FUND

Assets and Liabilities, December 31, 1943

Current Assets

Cash in banks	$ 1,937.18	
Accrued Income	1,357.09	
Investments at book value (cost)	144,787.36	
Total	$148,081.63	
Endowment Fund Principal		$146,724.54
Accrued Income, due General Fund		1,357.09
		$148,081.63

Endowment Fund Operation

Endowment Fund Principal, January 1, 1943		$136,329.06
Add:		
Life Membership Fees received during 1943	$ 7,285.00	
Transfer of Initiation Fees of New Life Members from General Fund	2,510.00	
Net Gain from Sale of Endowment Fund Investments	600.48	10,395.48
		$146,724.54

Endowment Fund Income

Income from Endowment Fund Investments earned in 1943		$ 4,508.46
Less		
Research Fellowship	$ 2,100.00	
John Phillips Memorial Prize, none		2,100.00
Excess transferred to General Fund Operations for 1943		$ 2,408.46

EXHIBIT "B"

Summary of Operations, Year Ending December 31, 1943

Income:				
Annual Dues			$ 25,164.97	
Initiation Fees			13,944.78	
Subscriptions, Annals of Internal Medicine			32,863.45	
Advertising, Annals of Internal Medicine			11,744.02	
Income from Investments, General Fund			5,413.21	
Income from Investments, Endowment Fund			4,508.46	
Profit on Keys, Pledges and Frames			135.56	
Profit, Sales, Furniture and Equipment			.87	
Dividends, Perpetual Insurance Deposit			60.00	
Sales, 1941 Directory and College History			6.10	
Rent, Real Estate, 404 S. 42nd St.		$ 1,800.00		
Less Maintenance on above	$104.82			
Insurance on above	18.00			
Taxes on above	489.55	612.37	1,187.63	$ 95,029.05
Expenditures:				
Salaries			$ 25,487.15	
Postage, Telephone and Telegraph			3,608.20	
Office Supplies and Stationery			1,215.25	
Printing			23,486.85	
Traveling Expenses			2,834.55	
Miscellaneous Expenses			1,103.06	
College Headquarters:				
Maintenance		$ 1,933.29		
Heat, Light, Gas and Water		796.88		
Taxes		860.07		
Insurance		156.01		
Depreciation on Building		1,000.00	4,746.25	
Depreciation on Furniture and Equipment			878.35	
War-Time Graduate Medical Meetings		$ 5,000.00		
Less Reserve transferred from Directory Reserve		2,000.00	3,000.00	
Research Fellowships			2,100.00	
Investment Counsel and Custodian Fees			391.47	
Regional Meetings			4,075.83	
Postgraduate Courses, 1943			810.36	
Collection and Exchange			19.47	
Loss on Sale or Maturity of Investments, General Fund			283.61	
1943 Membership Roster		$ 1,405.94		
Less Reserve transferred from Directory Reserve		500.00	905.94	
U. S. Taxes			160.99	75,107.33
Net Income, Year 1943				$ 19,921.72
General Fund				
Balance, January 1, 1943			$190,569.76	
Less Transfer to Endowment Fund, Initiation Fees of New Life Members			2,415.00	188,154.76
Total, General Fund				$208,076.48

EXHIBIT "C"

Detailed Statement of Operation for Year Ending December 31, 1943

General Fund

Income

Annual Dues		$ 25,164.97	
Initiation Fees		13,944.78	
Income from General Fund Investments		5,413.21	
Profit, Sale of Keys, Pledges and Frames		135.56	
Dividends on Perpetual Insurance Dep.		60.00	
Sales, 1941 Directory and College History		6.10	
Rent		1,800.00	
Net Profit, Sale of Furniture and Equipment		.87	$ 46,525.49

Expenses

Executive Secretary's Office

Salaries	$16,341.19		
Communications	2,120.65		
Office Supplies and Stationery	696.65		
Printing	1,183.55		
Maintenance	22.15		
Traveling Expenses	2,523.15		
Miscellaneous	603.52	$ 23,490.86	

College Headquarters

Maintenance	$ 1,933.29		
Heat, Light, Gas and Water	796.88		
Insurance	156.01		
Depreciation	1,000.00		
Taxes	860.07	4,746.25	

Other Expenses

Investment Counsel Service	$ 200.00		
Security Custodian Fees	191.47	391.47	
Depreciation Furniture and Equipment		878.35	
Postgraduate Courses		810.36	
Regional Meetings		4,075.83	
War-Time Medical Meetings	$ 5,000.00		
Less Reserve (transferred from Directory Reserve)	2,000.00	3,000.00	
Collection and Exchange		19.47	
Loss on Sale or Maturity of Investments		283.61	
1943 Membership Roster	$ 1,405.94		
Less Reserve (transferred from Directory Reserve)	500.00	905.94	
U. S. Taxes		160.99	

President's Office

Salaries	$ 50.00		
Postage	35.00		
Traveling Expenses	296.56	381.56	

Real Estate, 404–12 S. 42nd St.

Maintenance	$ 104.82		
Insurance	18.00		
Taxes	489.55	612.37	39,757.06
General Operation Profit			$ 6,768.43

Income

Subscriptions		$ 32,863.45	
Advertising			
Volume 18	$ 5,395.35		
Volume 19	6,356.72		
	$11,752.07		
Less adv. Vol. 17	8.05		
Total		11,744.02	$ 44,607.47

Expenses

	Ex. Sec'y	Ed. Off.	Total	
Salaries	$ 2,915.96	$ 6,180.00	$ 9,095.96	
Communications	1,233.21	219.34	1,452.55	
Office Supplies and Stationery	488.05	30.55	518.60	
Printing	22,303.30		22,303.30	
Miscellaneous	212.99	4.40	217.39	
Traveling Expenses		14.84	14.84	
Editorial Assistance		260.00	260.00	33,862.64
	$27,153.51	$ 6,709.13		
Net Profit, ANNALS OF INTERNAL MEDICINE				$ 10,744.83

Endowment Fund Income

Income from Investments	$ 4,508.46	
Less Research Fellowship	2,100.00	
Excess, General Fund		$ 2,408.46
Net Income from General Operation		6,768.43
Total Net Profits, 1943		$ 19,921.72

SCHEDULE I—INVESTMENTS

December 31, 1943

Par Value	Bonds	Endowment Fund Investments	General Fund Investments	
$ 5,000	Carolina Clinchfield & Ohio Ry., 1st Mort., Series "A," 4s, 1965	$ 5,125.00		
5,000	Chicago Burlington & Quincy RR Co., Gen., 4s, 1958		$ 4,893.75	
5,000	Chicago & Western Indiana RR Co., Consol., 4s, 1952	5,225.25		
5,000	Consolidated Edison Co. of N. Y., Inc., Deb., 3½s, 1956		5,244.62	
10,000	Federal Farm Mortgage Corp., 3s, 1944–49		10,875.00	
8,000	Florida Power & Light, 1st Mort., 5s, 1954	8,376.25		
5,000	Great Northern Railway, Gen. Mort., Series "B," 5½s, 1952	4,463.45		
5,000	New York, New Haven & Hartford RR Co., Harlem River & Port Chester, 1st, 4s, 1954		5,175.00	
5,000	Ohio Edison Co., 1st Mort., 4s, 1965	5,287.50		
4,000	Ohio Public Service, 1st Mort., 4s, 1962	4,240.75		
6,000	Pennsylvania Company Trust Certs., Guaranteed, Series "E," 4s, 1952		6,465.81	
5,000	Pennsylvania RR, Gen. Mort., Series "E," 4¼s, 1984	5,013.10		
5,000	Philadelphia Company Collateral Trust S. F., 4¼s, 1961	5,125.00		
64,000	U. S. Treasury Defense Bonds, Series "G," 2½s, 1953	64,000.00		
2,000	U. S. Treasury, 4s, 1944–54	1,998.13		
10,400	U. S. War Savings Bonds, 2½s, Series "G," 1955	10,400.00		
$149,000	TOTAL, Bonds	$119,254.43	$ 32,654.18	
Shares	Stocks			
50	American Brake Shoe & Foundry Co., Conv. Pfd.		$ 6,163.60	
100	American Gas & Electric Co., 4¾s, Cum. Pfd.		10,887.62	
50	Atchison, Topeka & Santa Fe, 5%, Pfd.		4,970.75	
100	Chase National Bank of New York		4,550.00	
100	Curtiss-Wright Corp., Class A		2,652.80	
25	Eastman Kodak Co., Common		4,200.38	
75	General Motors Corp., Common		3,594.53	
40	Great Atlantic & Pacific Tea Co., 7%, 1st, Cum. Pfd.		5,133.75	
50	Gulf States Utilities, $6.00, Cum. Pfd.		5,628.00	
100	Hercules Powder Co., 6%, Cum. Pfd.		12,935.50	
50	International Harvester, 7%, Cum. Pfd.	$ 8,169.00		
100	International Nickel Co. of Canada, Ltd.		3,825.85	
10	Johns-Manville Corp., 7%, Cum. Pfd.	1,266.77		
50	Monsanto Chemical Co., Series "A," $4.50, Cum. Pfd.	5,878.60		
50	Montgomery Ward & Co., Inc.		2,594.75	
150	Pacific Gas & Electric Co., 6%, Pfd.		4,640.50	
50	J. C. Penny Co.		4,084.90	
200	Philadelphia Electric Co., $1.00, Pref. Common	4,943.75		
100	Phillips Petroleum Co., Common		3,978.80	
55	Texas Company	2,746.48		
50	Timken Roller Bearing Co.		3,407.25	
30	Union Carbide & Carbon Corp.	2,528.33		
	TOTAL, Stocks	$ 25,532.93	$ 83,248.98	
	TOTAL, Investments	$144,787.36	$115,903.16	$260,690.52

OBITUARIES

DR. OSWALD EVANS DENNEY

With the death of Dr. Oswald Evans Denney on February 19, 1944, the U. S. Public Health Service lost one of its most competent and loyal officers. For thirty years his life was devoted essentially to public health work. Both the medical profession and the Service lost an outstanding leprologist.

Dr. Denney was born at Smyrna, Delaware, on July 21, 1885. He took his premedical work at the University of Pennsylvania and received the degree of Doctor of Medicine from the university's Medical School in June 1913. During the following two years, he served a rotating internship at the Philippine General Hospital and the Bureau of Science in San Lazaro Hospital, Manila. At the same time he studied at the University of the Philippines, earning the degree of Doctor of Tropical Medicine in 1915.

Dr. Denney had a most interesting professional career. Immediately upon finishing his internship he was appointed resident physician to the Culion Leper Colony, Culion, Philippine Islands, and three months later he was made chief medical officer of the Colony. During the next four years, he studied leprosy in all of its phases among more than 5,000 patients and did research work of exceptional value. He also did special work in the hospitalization and treatment of cases of Asiatic cholera, smallpox, and bubonic plague.

In July 1919, Dr. Denney was appointed Acting Assistant Surgeon in the U. S. Public Health Service, and two months later was commissioned as Passed Assistant Surgeon in the Reserve. He was assigned as executive officer to the Fourth District office at San Francisco, California to assume charge of the examination and treatment of veterans of World War I.

Negotiations were then in process for the Government's purchase of the Louisiana State Leprosarium at Carville. Dr. Denney was active in planning the remodeling of this institution which was to become the National Leprosarium, a hospital of the Public Health Service for the care of all lepers in the United States. Dr. Denney was the first officer in charge of the National Leprosarium. He was appointed to this post on September 22, 1920, and served until November 1, 1935. He was a delegate to the Pan American Leprosy Conference at Rio de Janeiro, Brazil, in the fall of 1922.

During the fifteen years that Dr. Denney spent at Carville, he was instrumental in building the National Leprosarium from a 90-bed wooden structure to a modern fireproof hospital and home capable of taking care of 425 lepers. He was, however, more than an administrator in that he took a personal interest in all the patients, following closely their medical and surgical treatments and their physical progress. He recognized that the treatment of leprosy meant more than giving medicinal aids. He felt that recovery from the disease largely depended upon the complete adjustment to the difficult

conditions brought about by compulsory isolation. To accomplish this, he employed every patient physically capable of performing regular duties, and provided extensive recreational facilities, including a motion picture theater, recreation hall, golf course, and tennis, soccer and basketball courts. He also encouraged self-government by the patients. His remarkably able and happy administration of the National Leprosarium seems a special achievement of the Service.

By reason of his observations and research work, Dr. Denney was able to make many contributions toward furthering the knowledge of leprosy. He was thoroughly conversant with the disease in other countries, traveling in Japan, China, the Philippine Islands, and South America to study the disease.

Dr. Denney's personal interest in leprosy was always in the foreground. He spent his personal funds to collect a large library on the disease and prepared an excellent exhibit, consisting of photographs, many in color, illustrating various manifestations of leprosy. This exhibit, which won the bronze medal of the American Medical Association in June 1928, was shown by Dr. Denney before many medical societies and medical colleges where he lectured.

To the members of his staff at Carville, both scientific and professional, Dr. Denney was more than a commanding officer. He was wise in counselling, slow to anger, and democratic in administration. His attributes encouraged confidence and faithful observance of duties.

In April 1936, Dr. Denney went to the Panama Canal Zone to assume the duties of Chief Quarantine and Immigration Officer of the Canal Zone and consultant to the health department. During the three years he served in this post, he kept up his interest in leprosy by making frequent trips to the Leper Colony on the Island of Palo Seco. On July 1, 1939, he was promoted to Senior Surgeon in the Regular Commissioned Corps.

At the request of the Pan-American Sanitary Bureau, Dr. Denney acted as consultant to the Government of San Salvador in April 1940 to formulate a plan for the general reorganization and coördination of the hospitals and other social services of that country. In July of that year he was assigned as medical officer in charge of the Marine Hospital at Galveston, Texas, and chief quarantine officer for the Port of Galveston. He retained these positions until his death. He died of pulmonary fibrosis due to old pulmonary disease, following a year of gradually failing health and an attack of influenza at Christmas time.

Dr. Denney was a Fellow of the American College of Physicians and the American Medical Association; member of the American Society of Tropical Medicine, Association of Military Surgeons of the United States, International Leprosy Association, American Legion, Phi Chi, Sigma Xi, and the Medical Advisory Board of the Leonard Wood Leprosy Memorial. His writings include more than thirty articles on medical topics, chiefly leprosy.

Dr. Denney's record in the Public Health Service was meritorious. We in the Service deeply regret his passing.

THOMAS PARRAN, M.D., F.A.C.P.,
Surgeon General, U. S. Public Health Service.

DR. DOUGLAS HAMILTON MEBANE

On November 12, 1943, at Brooke General Hospital, Fort Sam Houston, Texas, Colonel Douglas Hamilton Mebane, Medical Corps, United States Army, died of cerebral hemorrhage following an illness of more than a year.

Colonel Mebane was an outstanding clinician of the Army, as his successive assignments indicate.

He was born in Lockhart, Texas, April 5, 1887. Here he spent his youth. He attended Austin College, Sherman, Texas, where he was graduated with an A.B. degree in 1911. Subsequently, he studied medicine and was graduated from the School of Medicine, University of Texas, in 1916. Following a year's internship at John Sealy Hospital in Galveston, Texas, he entered the military service as a First Lieutenant of the Medical Reserve Corps, July 19, 1917. Shortly thereafter he took the examination for and was commissioned in the Medical Corps of the Regular Army. He served overseas in France during World War I participating in numerous offensives. It was during the Chateau Thierry offensive that Colonel Mebane was cited for extraordinary heroism and awarded the Silver Star decoration. Later on while serving as a medical officer with the 10th Field Artillery during October, 1918, he was wounded and was awarded the Purple Heart.

In 1922, he attended the Army Medical School from which he graduated as an honor student.

He passed successively through the grades of Captain, Major, Lieutenant-Colonel, and was commissioned Colonel in 1942. His interest always was in internal medicine and he early became the Chief of Gastro-enterological and Metabolic Sections at Letterman General Hospital. Later he was assigned to the same services at William Beaumont General Hospital. Prior to the latter assignment, he took a postgraduate course in gastrointestinal diseases at the Mayo Clinic, Rochester, Minnesota. It was while serving as Chief of the Medical Service, Tripler General Hospital, Honolulu, Hawaii, that the writer had his closest contact with Colonel Mebane. Upon his return to the continental United States, Colonel Mebane was assigned as Chief of the Medical Services at the Station Hospital, Ft. Leavenworth, Kansas.

The last assignment, prior to his retirement from the Service for physical disability, was as Chief of the Medical Services, Billings General Hospital, Indianapolis, Indiana. It was while serving temporarily as Commanding Officer at that station that Colonel Mebane experienced his first cerebral accident, necessitating his retirement from active duty. Colonel Mebane was elected to Fellowship in the College in 1932.

Colonel Mebane was an assiduous student, a clinician of high attainment, conscientious, a true and loyal friend, a man who, though tender and sympathetic, nevertheless knew how to be firm when the best interest of his patients demanded such action. Though a big man physically, he was soft spoken and gentle.

He is survived by his wife (Coralie West), his son Douglas, Jr., and two sisters.

His many friends will remember Colonel Mebane as a kindly man and a "doctor" in the highest meaning of that word.

EUGEN G. REINARTZ, F.A.C.P.,
Brigadier General, (MC), U. S. A.

DR. JACOB CARL KRAFFT

Dr. Jacob Carl Krafft, F.A.C.P., late of Chicago, was born at Napoleon, Ohio, November 26, 1874. He received his A.B. degree in 1896 from Northwestern University, Watertown, and his M.D. degree from Long Island College Hospital, Brooklyn, in 1899. He was Instructor in Pediatrics at the University of Illinois, 1903–11, and Professor of Pediatrics at the Chicago Polyclinic, 1915–20. He did postgraduate study in Pediatrics at Bellevue Hospital, New York City, and in Vienna. He was Attending Pediatrician to the City of Chicago Municipal Tuberculosis Sanitarium, 1905–09; for many years Clinical Professor of Pediatrics at Loyola University School of Medicine and Attending Pediatrician to the Norwegian-American, Garfield Park and Walther Memorial Hospitals. He was a former President of the Illinois State Medical Society, a Fellow of the American Academy of Pediatrics, the American Medical Association and the American College of Physicians (1917). He was also a Diplomate of the American Board of Pediatrics. During World War I he served as Major, Medical Corps, U. S. Army. Dr. Krafft died March 28, 1944, at his home in Oak Park, Ill., of coronary thrombosis, at the age of 69.

Dr. Krafft was very personally known to the undersigned since 1903, at which time he was a member of the Pediatrics Department of the University of Illinois College of Medicine. He served in this capacity until he accepted a position as Clinical Professor at Loyola University School of Medicine. He was an excellent teacher, a skilled physician and a most sympathetic man in the practice of his specialty. Besides his teaching and his very active practice, he also gave much time to civic activities. It was through Dr. Krafft's individual efforts that the Handicapped Children's Commission of Illinois enacted a program under its auspices for the education of mentally handicapped children. This is probably the most outstanding fight made by Dr. Krafft for the underprivileged child (all expenses of this effort were borne by him personally).

JULIUS H. HESS, M.D., F.A.C.P.,
Chicago, Ill.

DR. ALBERT FRANKLIN TYLER

Dr. Albert Franklin Tyler, F.A.C.P., died in Omaha on February 25, 1944, of coronary occlusion. He was born in Logan County, Illinois, on March 14, 1881. He received his B.S. degree from Nebraska Wesleyan University in 1904, and his M.D. degree from Creighton University in 1907.

After a few years in general practice Dr. Tyler limited his work to Roentgenology. Deeply interested in medicine and an excellent teacher, he was Professor of Clinical Radiology at his Alma Mater from 1917 to 1933. He was a member, and past president, of the Omaha-Douglas County Medical Society, a Fellow of the A. M. A., a member of the American Roentgen Ray Society, the British Roentgen Society, the Omaha Mid-West Clinical Society, and a Fellow of the American College of Physicians. He served as President of the Radiological Society of North America in 1920, President of the American Congress of Physical Therapy in 1933. At the time of his death he was President of the Nebraska Radiological Society.

Dr. Tyler was a prolific writer. He was author of many scientific publications and two books, one of which, a history of medicine in Nebraska, he compiled and published at his own expense in 1928. This service to the profession of Nebraska was of inestimable value, and is sure to remain a monument to his name. For many years until the time of his death he contributed his wise counsel to the Nebraska State Medical Journal as a member of its Publications Committee. He served as Editor of the Journal of Radiology in 1921–22, managing editor of The Archives of Physical Therapy from 1923 to 1930.

Dr. Tyler contributed freely and willingly of his time to civic activities as a member of the Methodist Church, the Y. M. C. A., the Rotary Club and the Chamber of Commerce. For years he served on the Board of Trustees of the Nebraska Wesleyan University.

His life was full and varied. In spite of failing health in recent years, he gave of himself in service to others. In the death of Dr. Tyler the profession has lost an able, tireless worker and the community a lovable, conscientious citizen of high ideals.

WARREN THOMPSON, M.D., F.A.C.P.,
Governor for Nebraska

DR. ROY ALBERT HILL

Dr. Roy Albert Hill, F.A.C.P., Thomasville, Ga., was born in Mitchell County, Ga., March 14, 1889. He received his medical degree from Emory University School of Medicine in 1915 and interned at the Greenpoint, New York, Hospital, 1915–18. He did postgraduate work in cardiology at the New York Post-Graduate Medical School and Hospital. For many years he was a senior member of the medical staff of the John D. Archbold Memorial Hospital.

Dr. Hill was formerly President of the Thomas County Medical Society, a member of the Georgia State Medical Society, the Southern Medical Association and the American Medical Association. He had been a Fellow of the American College of Physicians since 1929. His death occurred on January 1, 1944, due to coronary thrombosis; aged fifty-four.

DR. JOHN COX WALL

Dr. John Cox Wall, F.A.C.P., Eastman, Ga., was born at Macon, Ga., November 23, 1882. He removed to Eastman at an early age and after completing his medical education at the Atlanta College of Physicians and Surgeons, 1907, and postgraduate work at the New York Post-Graduate Medical School and Hospital, he spent the balance of his life in this locality. At various times he left for short periods for postgraduate work at the New York Polyclinic Medical School and Hospital, the Pediatric Seminar at Sulada, N. C., the Mayo Clinic, and at Tulane University. For many years he operated the Clinic Hospital; from 1922 to 1927 he was Vice Councilor of the Medical Association of Georgia; from 1927 to 1935, Councilor; from 1935 to 1943, Vice Councilor. He was a former Treasurer of the Georgia Pediatric Society, former Secretary and former President of the Ocmulgee Medical Association; a member of the Southern Medical Association and of the American Medical Association. He had been a Fellow of the American College of Physicians since 1938.

Dr. Wall died May 18, 1943, of heart disease; aged sixty-one years.

DR. MAURICE FRANCIS DWYER

Dr. Maurice Francis Dwyer died February 28, 1944, of cerebral apoplexy.

Dr. Dwyer was born March 10, 1889, in St. Louis, Missouri, and much of his boyhood was spent in Dawson, Yukon Territory. He graduated from Gonzaga University in 1910 with a degree of Bachelor of Arts; he then attended St. Louis University where he received the degree of Doctor of Medicine in 1914. He was licensed to practice in the State of Washington in 1914 and interned at Providence Hospital at Seattle. After internship he associated himself in practice with the late Dr. J. Tate Mason. He became interested in radiology and was an early and distinguished member of that specialty group, serving years ago as radiologist in the King County Hospital.

During the period following World War I, when there was a vital urge for betterment in clinical medicine and improvement in hospital facilities, his was a large part in the construction of the Virginia Mason Hospital and formation and direction of the Mason Clinic. These associations were terminated only by his death. On June 17, 1920, Dr. Dwyer was married to Madeline Mary Mitchell and they had two daughters, Margaret Mary and Frances Madeline.

Dr. Dwyer was a member of the King County Medical Society, Washington State Medical Association, American Medical Association, Washington State Radiological Society, Fellow of the American College of Physicians, Fellow of the American College of Radiology, member of the radiological Society of North America, and diplomate of the American Board of Radiology.

He was an indefatigable worker and possessed of a keenly inquiring mind; he contributed freely to local and national scientific journals.

No one knows or has ever said evil of him. He was kindly, fair and open-minded, and blessed with a sunny disposition, which illness failed to spoil. His relations with his family, his patients, his professional and business associates and the world in general, were nearly ideal. The passing of one with his ideals and principles is a great loss to a world in need of such men.

E. G. Bannick, M.D., F.A.C.P.,
Acting Governor for Washington

DR. HARRY S. BERMAN

Dr. Harry S. Berman, an Associate of the College, died at Harper Hospital, Detroit, February 16, 1944.

Dr. Berman, who was born in Baltimore, Maryland, January 17, 1899, received his M.D. from the College of Physicians and Surgeons, Baltimore, in 1914. Following this he did postgraduate work in Vienna and Prague, and later confined his work to pediatrics. He had been Attending Physician at St. Mary's Hospital, and a member of the staff of Harper Hospital. He also did important work for the Detroit Board of Health. He was a member of the Wayne County Medical Society, Detroit Pediatric Society, Michigan State Medical Society, American Medical Association, and the American Public Health Association. He was a diplomate of the American Board of Pediatrics.

During World War I he was a Captain in the Medical Corps in the United States Army, and later served on President Hoover's Food Commission, taking special interest in the rehabilitation of Czechoslovakia. Although his age and physical disabilities made him unfit for active duty in World War II, he continued his loyal service to his country by working consistently and diligently in the examination of draftees. His death marks the passing of a loyal citizen to his country and a faithful friend to his colleagues and patients.

P. L. Ledwidge, M.D., F.A.C.P.,
Acting Governor for Michigan

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